Association of Maternal Cumulative Risk during Pregnancy and IQ in Preschoolers: Role of Glucocorticoids and their Receptors

Katherine A. Beckmann

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ABSTRACT

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Katherine A. Beckmann

There may be a cumulative effect of social and environmental risk factors which lead to chronic, elevated levels of stress. Constant elevations of maternal stress hormones during pregnancy disrupt developing fetal brain chemistry and architecture, resulting in later memory and learning deficiencies. While we know that the quality of the fetal environment and the timing of exposure to a variety of substances are critical for developmental and health outcomes, little is known about the consequences of maternal cumulative risk on the fetus and later cognitive development. With data from the Nurse Family Partnership Elmira Sample, this work investigates whether maternal cumulative risk during pregnancy predicts IQ in 3 and 4 year olds, without and with postnatal influences. The role that birth outcomes play as mediators of this relationship is also explored. Finally, moderation effects and cumulative genetic risk of five polymorphisms of the glucocorticoid receptor (GR) gene are examined.

Increased maternal cumulative risk during pregnancy was negatively associated with IQ at ages 3 and 4 with and without the inclusion of postnatal controls. Birth outcomes partially mediated this relationship to a small extent. GR rs6198 G and rs6190 G alleles infer risk while rs6198 A alleles serve as protective factors with respect to the association of maternal cumulative risk during pregnancy and IQ in young children. This study contributes insights on the cumulative effects of chronic social and environmental stressors that may lead to increased levels of maternal stress hormones during pregnancy and poor cognitive outcomes in young children in the presence of specific glucocorticoid receptor single nucleotide polymorphisms. Application of findings to early intervention programming and policy is discussed.

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Dedication

To my parents…thank you for being my first teachers, always believing in me and that which I am capable, and forever filling my life with love. Grammy would have been proud.

Economic hardship has been linked to a myriad of adverse educational and developmental outcomes for children that limit future productivity (Barnett, 1998; Brooks-Gunn & Duncan, 1997; Wulczyn, Barth, Yuan, Jones Harden, & Landsverk, 2005). Today, with nearly 15.5 million children living in families with incomes below the federal poverty level ($22,050 per year for a family of four in 2009), almost 21% of America's children are at-risk for untoward psychosocial, environmental, and economic conditions compared to their wealthier counterparts (Brooks-Gunn & Duncan, 1997; Child Trends, 2010; DeNavas-Walt, Proctor, & Smith, 2011). Further, families with low socioeconomic status (SES) report greater exposure to multiple stress factors and more severe stressful life events than those of higher socioeconomic status (Liaw & Brooks-Gunn, 1994; Lupien, King, Meaney, & McEwen, 2000).

Consequently, there may be a cumulative effect of social and environmental risk factors, similar to that of chemical and biological environmental risks, which lead to chronic, elevated levels of stress and may be an important pathway linking socioeconomic status to health and developmental outcomes throughout the lifespan (Evans & Kim, 2010; Hackman, Farah, & Meaney, 2010; MacArthur Research Network on Socioeconomic Status and Health, 2005). Often measured by somatic hormones such as glucocorticoids, chronic, elevated levels of stress are associated with innumerable biologic and behavioral consequences that negatively affect physical growth, onset and duration of puberty, metabolism, susceptibility to illness, as well as social-emotional and cognitive functioning (Bradley & Corwyn, 2002; Center on the Developing Child at Harvard University, 2007; Harris & Seckl, 2011; McEwen & Seeman, 1999; McEwen & Stellar, 1993; Seeman, Berkman, Blazer, & Rowe, 1994; Welberg & Seckl, 2001).

Although research has addressed the association of early life stress exposure and later physical and mental health outcomes, less attention has been focused on the effects of early life stress exposure during the prenatal period and cognitive outcomes later in life. With respect to neurodevelopment, in particular, it is clear that no singular environmental factor can explain the effects of SES (Hackman, Farah, & Meaney, 2010). For children from low income families, especially, there may be both an exogenous influence on cognitive development stemming from stress associated with poverty post birth and an endogenous influence originating from maternal emotional state during pregnancy (Hackman, Farah, & Meaney, 2010; Oitzl et al., 2010; Van den Bergh, Mulder, Mennes, & Glover, 2005). Leading to vulnerabilities in utero as well as later in the child's life, constant elevations of maternal stress hormones during pregnancy may disrupt developing brain chemistry and architecture (Barker, 2007; Center on the Developing Child, 2007; Welberg & Seckl, 2001). With respect to postnatal cognitive development, altered stress hormone secretion in early childhood due to prenatal plasticity and adaptation may lead to decreased dendritic branching, neuronal loss in the CA3 area of the hippocampus, changes in synaptic terminal structure, and inhibition of neuron regeneration. Deficiencies in memory and learning capabilities may result (McEwen & Seeman, 1999).

But, why do some children who develop in similar environments flourish in ways that others do not? Although many processes by which the extra and intrauterine environment affect biology have yet to be clarified, more is known about the environmental risks and protective factors than genetic ones. Biological susceptibility to the influences of stress hormones is dependent upon the important relationship of stress hormones, their receptors, and the genetic instructions that give rise to these proteins (Oitzl et al., 2010). Imbalance in stress regulation, as a result of gene-environment interactions early in life, is characteristic of phenotypic

vulnerability to later life stressors and disorder (Oitzl et al., 2010). Although most supporting evidence has been studied after birth and primarily in animals, this is particularly important during the perinatal period when stress sensitivity is great (Meaney et al., 2007; Oitzl et al., 2010). In moving towards a better understanding of how stress and the actions of stress hormones, particularly glucocorticoids, move from less protective to more harmful, examining the fetal development in the context of genotypic and phenotypic variance is crucial.

From a policy standpoint, understanding potentially modifiable social environmental risk factors which interact with biological ones is essential when thinking about effective prevention strategies targeted toward families that address the negative consequences of stress on child health and development. While wear and tear on the body due to chronic stress and/or "weathering" has been quantified in terms of allostatic load by physiological measures, such as blood pressure, cortisol, and heart rate, an empirical measure of the cumulative risk that leads to allostatic load has not reached consensus, per se. Allostatic load has been shown to accelerate biological processes that give rise to disease and disorder throughout the lifespan (McEwen, 2000). As a result, biological and social science can support the development of cost-effective, targeted policy and prevention strategies to mitigate identifiable antecedents of allostatic load while promoting protective factors during the earliest stages of development when plasticity is greatest. Both positive and negative impacts on early brain development during gestation must be fully understood as we prepare our most vulnerable children to attend school, ready to learn.

Biological Vulnerability Affecting Cognitive Development

The fundamental architecture for cognitive functioning is related to neuronal formation and the developing network of neural connections. By the time a full-term infant is born, the basic wiring of the central nervous system has been completed. The prenatal establishment of brain architecture provides the scaffolding on which one later builds the capacity to receive, interpret, and act upon information gathered from the surrounding world (Hammock & Levitt, 2006). Precursors of functional brain regions manifest during the first and second trimesters when neurons are produced and regional migration occurs. The fine-tuning of circuits within these regions takes place after birth through experience-dependent mechanisms such as synapse formation and pruning (Bourgeouis, Goldman-Rakic, & Rakic, 1999). Consequently, intra and extra-uterine exposures such as drugs, alcohol, toxins, and inflammatory responses (Fox, Levitt, & Nelson, 2010; Stanwood & Levitt, 2008) may disrupt early regulatory gene networks and neuronal guidance cues. The resulting abnormal connections may have immediate and enduring impacts on neural circuitry. Long-term implications may include disruption of cellular differentiation as well as cognitive and behavioral development in childhood (Bourgeouis et al., 1999). While genes dictate much of the biological processes which aid in neurodevelopment from conception, the intrauterine environment acts as an intermediary through which the genetic blueprint is translated. Prenatal programming of the brain is sensitive to growth factors, nutrients, transcription factors, and steroids such as glucocorticoids (Center on the Developing Child, 2007; Welberg & Seckl, 2001).

Expressed in almost all human tissues and cells, glucocorticoids play an important role in the endocrine control of homeostasis; metabolism; blood pressure; immune functions; neuronal function and behavior; cell growth and differentiation; as well as cell survival in some tissues and cell death in others (Meaney, 2010; Seckl & Holmes, 2007). At later stages of normal

human pregnancy, fetal exposure to a prepartum surge of circulating cortisol, the most common type of human glucocorticoid, is necessary for lung, liver, and kidney maturation as well as fetal preparation for birth (Gluckman & Hanson, 2005). The surge is also critical for normative brain and neuroendocrine development in utero (Austin & Leader, 2000; King, Nicholson, & Smith, 2001; Liggins, 2000; Welberg & Seckl, 2001). In addition to this spike, moderate levels of glucocorticoids are important in general brain development, behavior regulation, and increased neural plasticity after birth (Catalini et al., 2002).

Although individuals differ in their physiological responsiveness and range in ability to adapt to their environment, glucocorticoids are released when neural signals detecting immediate stressors are increased (Sapolsky, Romero, & Munck, 2000). As the source of "fight or flight" response in the human body, these hormones increase the accessibility of energy which aids in the maintenance of cellular function and organ efficiency and acts as a protection against biological crisis (Meaney, 2010). While protective in acutely stressful contexts, the neurobiological and behavioral responses mobilized by the endocrine system throughout the lifespan can become maladaptive and pathogenic if consistently activated under chronic, overwhelming stress and adversity (McEwen & Seeman, 1999).

Among the unfavorable effects of chronic, elevated levels of stress response and consequential hormones (e.g. glucocorticoids) on cognitive function are impaired hippocampal-dependent memory retention and retrieval as well as spatial memory in children and adults (McEwen, 2007). Of all human tissues, brain tissue is thought to be especially vulnerable to elevated oxidative stress as a result of glucocorticoids (Costantini, Marasco, & Moller, 2011). Further, research has shown that younger individuals are even more susceptible to

glucocorticoid-induced oxidative stress (Wada et al., 2008). Oxidative stress may compromise functionality, increase vulnerability to progressive damage, and be associated with the presence of neurodegenerative disorders (Oitzl et al., 2010). Acting via glucocorticoid receptors, glucocorticoids can damage neural plasticity (Gunnar & Quevedo, 2007). In animal models, chronic, elevated levels of glucocorticoids appear to be detrimental in terms of decreased hippocampal, prefrontal cortical, and amygdalar volume; increased stress biological reactivity; and poor performance on cognitive tasks (Brabham et al., 2000; Hauser et al., 2007; Uno et al., 1994; McEwen, 2007).

Research on cognitive development in animal models. For the most part, research on prenatal stress and developmental processes has been based in rodent and nonhuman primate studies (Fox & Rutter, 2010). However, there are key translational issues when taking lessons learned from rodent models and applying them to humans (Glover, O'Connor, & O'Donnell, 2010). The effects of experiences on brain development depend on timing, frequency, and duration. At birth, the rodent brain is much less mature than the human brain. Histogenesis, or cell differentiation of specified cells from non-specified ones, of neurons in the human central nervous system begins 56 days after conception and continues throughout the first years of life. The initial cell differentiation and axon guidance occurs comparatively early and quickly with completion by mid-gestation in primates and the end of gestation in rodents (Levitt, 2003). The differences in reproductive physiology are especially important when considering the amount of research in early human developmental processes based on studies of rodents (Power, et al., 2006). In fact, the first postnatal week for rodent pups could equate to the third trimester of gestation for humans (Dobbing, 1981). This supports the need for additional longitudinal research on early experience and development during the prenatal period in human samples,

especially with regards to prenatal stress and long-term disturbance in endocrine function and cognitive development in children (Coe et al., 2003; Gunnar, Fisher, & The Early Experience, Stress, and Prevention Network, 2006; O'Connor et al., 2005).

Stress Hormones and Fetal Programming for Developmental Outcomes

While the human body's response to stress is essential for survival, changes to fetal endocrine, cardiovascular, metabolic, and behavior regulation resulting from chronic maternal stress may be beneficial for survival while in utero but not necessarily advantageous ex utero (Gluckman & Hanson, 2005; Meaney, et al., 2007; Oitzl et al., 2010; Welberg & Seckl, 2001). During pregnancy, stress, alcohol consumption, smoking, diminished protein intake, nutrient excess, placental insufficiency, and glucocorticoid exposure are examples of maternal environmental exposures which can modify fetal organ development and endocrine functioning (Collins, Dunkel-Schetter, Lobel, & Scrimshaw, 1993; Harris & Seckl, 2011; Kapoor et al., 2006; Simmons, 2008). Maternal cardiovascular and endocrine changes that include increases in plasma ACTH, β-endorphin, glucocorticoid, and catecholamine concentrations in the mother could also impact the developing fetus (Welberg & Seckl, 2001). Evidence also points to programming effects of stress hormones during preconception (de Kloet, E., Sibung, R., Helmerhorst, F., & Schmidt, M., 2005). Characterized by birth weight, gestational age, and head circumference, birth size is often used as a proxy for the fetal experience of the intrauterine environment (Gluckman & Hansen, 2005; Sandman, Davis, Buss, & Glynn, 2011).

Restriction of intrauterine growth acts as a protective mechanism for survival in utero (Seckl, Drake, & Holmes, 2005). For example, when the fetus does not get a sufficient amount of oxygen or nutrients from the intrauterine environment, it shuts down non-essential functions

and moves blood flow to the most important organs—the developing brain, heart, and placenta (Gluckman & Hansen, 2005). The fetus also changes its growth pattern and/or stops growing to conserve even more energy in order to strategically adapt and survive in both the short and long term (Gluckman & Hansen, 2005). In this regard, poor fetal nutrition and fetal exposure to excess glucocorticoids are typical causes of low birth weight and preterm birth as well as later vulnerability to disease and disorder (Barker, 2007; Kapoor et al., 2006; O'Connor et al., 2005; Power & Tardif, 2005; Seckl et al., 2005).

In addition to nutrition, social factors which influence maternal emotional well-being and stress, while altering the hormonal environment of pregnancy, may modify fetal endocrine function (Avishai-Eliner, Brunson, Sandman, & Baram, 2002; Wadhwa, Culhane, Rauh, & Barve, 2001; Welberg, Thrivikraman, & Plotsky, 2005). Although the placenta forms a structural and biochemical barrier to many maternal factors, some still enter the immediate environment of the fetus. A recent study has indicated that maternal stress during pregnancy can influence placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) activity (Welberg et al., 2005). 11β-HSD-2 regulates fetal cortisol exposure and forms a barrier to maternal glucocorticoids (e.g. cortisol) as protection during important early periods of development (Seckl, Cleasby, & Nyirenda, 2000; Welberg & Seckl, 2001). Since fetal glucocorticoid levels are much lower than maternal levels, subtle changes in placental 11β-HSD-2 activity may profoundly affect fetal glucocorticoid exposure by increasing transfer of maternal glucocorticoids (Seckl et al., 2000).

While exposure to maternal glucocorticoids is essential for normative organ and system development in late gestation, in earlier developmental periods it can lead to elevations in

postnatal child basal and stress-stimulated HPA activity (Power & Tardiff, 2005; Welberg et al., 2005). Increases in basal and stress-stimulated HPA activity, as well as resulting elevated levels of circulating cortisol, have been linked to an increased risk of subsequent disease and disorder (Seckl et al., 2000). In animal models, elevated glucocorticoids during egg production in the mother is associated with reduced growth, condition, and body size in offspring (Erikson et al., 2006; Meylan & Clobert, 2005). Further, prenatal exposure to elevated maternal glucocorticoid levels can program gene expression resulting in adverse influences on cardiovascular tone and reactivity; insulin sensitivity; production and storage of energy substrates (e.g. glucose and fat); birth weight; and programming of the central nervous system (Barker, 2007; Meaney et al., 2007). These effects increase the risk for hyperlipidemia, hyperglycemia, and hypertension, among other disorders. Similarly, prenatal stressors increase HPA responses to stress in later life, further augmenting the risk of metabolic disorders (Barker, 2007; Meaney, et al., 2007).

Evidence from animal models also suggests that exposure to maternal stress in utero can result in low birthweight and cognitive impairment later in life such as learning deficits, increased anxiety, and reduced attention span (Glover, O'Connor, & O'Donnell, 2010; Gutteling et al., 2006; Hosseini-Sharifabad & Hadinedoushan, 2007; Yang et al., 2006). In studies in which rats were subjected to stress throughout pregnancy, female rat pups born to prenatally stressed mothers have shown significantly decreased hippocampal glucocorticoid receptor (GR) density (Henry et al., 1994; Weinstock, Matlina, Maor, Rosen, & McEwen, 1992). Omnipresent in fetal tissues from early embryonic stages, glucocorticoid receptors influence the developing fetus when glucocorticoids bind, triggering a cascade of events important for survival (Harris & Seckl, 2011). Of particular note to cognitive development, fewer GR binding sites have implications for hippocampal negative feedback and termination of the pituitary–adrenal

response following activation (Rautanen et al., 2006). In other words, early life endocrine programming due to maternal stress during pregnancy results in pups with fewer GR binding sites and higher, persistent levels of circulating cortisol which could lead to impaired cognitive outcomes in early life. Other work has demonstrated that rats exposed to prenatal stress are more likely to have an accelerated and age-related decline in spatial and working memory (Vallee et al., 1999). Pre and perinatal administration of glucocorticoids to pregnant rodents has resulted in reduced brain weight at birth as well as delayed neuronal maturation, myelination, gliogenesis, and synapse formation (Seckl, 2008).

In animal studies on non-human primates, exposure to maternal stress during gestation has been associated with delayed object permanence in rhesus monkeys (Schneider, 1992). Prenatal exposure to elevated levels of glucocorticoids in rhesus monkeys has also been associated with reduced hippocampal volume later in life (Uno et al., 1989). In another study, female rhesus monkeys who were stressed during pregnancy gave birth to offspring that displayed decreased birthweight, impaired neuromotor development, attention deficits, and emotional dysregulation into adulthood (Schneider et al., 2002).

While high levels of stress reactivity and cortisol during pregnancy have placed children at higher risk for adverse developmental outcomes, these outcomes are not deterministic. Although the prenatal period is a critical time for development, times of sensitivity and programming extend beyond gestation. Postnatal social environmental risk factors can have an independent effect on the well-being of the child and magnify prenatal insults to stress reactivity and endocrine functioning (Meaney et al, 2007; Oitzl et al., 2010). These factors include extended maternal separation (e.g. isolated or deprived rearing conditions), parental divorce,

maternal mental illness, child abuse and neglect, and poverty (Gluckman & Hanson, 2005; Kapoor et al., 2006; Meaney et al, 2007).

Postnatal influences, such as social stimulation and nurturance, can mitigate the untoward effects of early life programming due to maternal stress during pregnancy (Liu et al., 2000; Maccari et al., 1995; Weaver, et al., 2005). Research has shown that maternal responsiveness and proximity may serve as protective factors, or buffers, that maintain basal cortisol levels during early development in rat pups (Adam, Klimes-Dougan, & Kudielka, 2007). Reversing cognitive impairment resulting from early exposure to life stress, environmental enrichment appears to support the capacity for cognitive restoration or protection (Hedges & Woon, 2011). In fact, the current differential susceptibility framework dictates that those vulnerable to adversity may also be most likely to benefit from supportive and enriching resources (Belsky et al., 2009).

Role of the Glucocorticoid Receptor Gene in Stress Hormone Regulation

Genetics 101. Genetic information is the blueprint for the structure and function of proteins that allow biological processes to occur. Everything in the human body from digestion to stress response takes place due to proteins employed in the maintenance of homeostasis. Nucleotide sequences within DNA give rise to RNA which in turn translates into proteins. Individuals may have the same types of genes but differ in DNA sequence. Each gene can have different alleles that result in similar or dissimilar expression and traits. Further, genetic causes of disorder and disease are thought to be rooted in structural variations of DNA at a given locus, or polymorphism (Ingles, 2004; Plomin, Defries, McClearn, & McGuffin, 2008; Ziegler & Konig, 2010).

With approximately 10 million recognized, single nucleotide polymorphisms (SNPs) are the most common type of polymorphism, or point mutation (DeRijk, 2009). Point mutations may result in transitions, substitution of one purine for another (A for G) or one pyrimidine for another (C for T); transversions, replacement of a purine by a pyrimidine and vice versa; missense mutation (changing one amino acid into another); or nonsense mutation (changing to a stop codon that does not allow chains of amino acids to form proteins). In addition, frame shift mutations resulting from the insertion of a nucleotide can completely change the amino acid sequence downstream of the mutation. The change in DNA sequence may or may not change the function or structure of the resulting protein (Ingles, 2004; Plomin et al., 2008; Ziegler & Konig, 2010). Even if a functional protein results, little is known about how protein products lead to phenotypes involving behavioral traits or disorders. To make things even more complicated, gene expression is specific to particular body tissues as well as certain phases of development (Rutter, M., 2006). SNPs can influence gene expression by influencing promoter activity, transcription efficiency, gene splicing, translation efficacy, and/or mRNA stability (DeRijk, 2009).

Glucocorticoids, Receptors, and Sensitivity. Glucocorticoids bind to receptors to form complexes which function both as transcription factors, themselves, and proteins that regulate

other transcription factors to preserve homeostasis in the body's stress response system (Colli, et al., 2007; Rautanen, 2006). In the brain, specifically, glucocorticoid receptors prevent initial cellular reactions to stressors from overshooting, allow cells to return to baseline levels, and facilitate recovery through energy metabolism (Oitzl, Champagne, van der Veen, & de Kloet, 2010). This continuing cycle of stress, recovery, and adaptation is essential in biological mechanisms that allow memory storage, for example (Oitzl et al., 2010).

In a recent study, Oitzl and colleagues posited that life programming by early experience and genetic foundations is controlled by GR-driven mechanisms (2010). Sensitivity to glucocorticoids has been shown to vary across populations and is somewhat dependent on polymorphisms within the glucocorticoid receptor gene (*GR* gene or NR3C1) (van Rossum, et al., 2004) (See Figure 1). Tissue-specific regulation of the GR gene during different developmental stages has been demonstrated. In fact, changes in GR gene regulation have been linked to a predisposition to disease vulnerability, particularly metabolic-related, cardiovascular, and brain diseases (DeRijk & de Koet, 2008).

While a large number of polymorphisms in *GR* gene are known, only a few have been found to be functional (Manenschijn, van den Akker, Lamberts, & van Rossum, 2009). Functional NR3C1 variants have impact on stress response system operation with lasting consequences for stress responsiveness and emotional arousal later in life (DeRijk et al., 2006; de Rijk, 2009; Murani et al., 2010; Oitzl et al., 2010). Deficits in GR activity have also modifed the effects of glucocorticoids in other targeted systems including metabolic, cardiovascular, and immune (DeRijk, 2009). For example, mutations in the glucocorticoid receptor gene have often caused glucocorticoid resistance which results in increased circulating glucocorticoids (DeRijk, Katraki, & de Koet, 2010; Spijker & van Rossum, 2009).

Some work in adult populations on metabolic syndrome has demonstrated an association between functional variants (rs6190, rs6198, and rs6189) and decreased sensitivity to glucocorticoids (van Rossum et al., 2004; DeRijk, 2009; Russcher et al., 2005; van Rossum et al., 2002) while others have demonstrated an association between SNPs (rs6195 and rs4142324) and increased sensitivity (DeRijk, 2009). Relevant to the current study and present in approximately 35% of the general population, the rs6198 polymorphism (A3669G) has been associated with increased GR β protein expression. The augmented expression is thought to have a negative effect on GR α transcriptional activity which results in glucocorticoid insensitivity (van Rossum, E. & van den Akker, E., 2011). In several studies, A3669G has been shown to be associated with the presence of rheumatoid arthritis, cardiovascular disease, and systemic lupus erythematosis as well as more favorable metabolic profiles in adult populations (Manenschijn, van den Akker, Lamberts, & van Rossum, 2009). Homozygous carriers appear to maintain hyperactive immune systems (DeRijk, Katraki, & de Koet, 2010).

Also associated with glucocorticoid insensitivity and pertinent to the current study, rs6189/rs6190 (ER22/23EK) polymorphisms have been found in approximately 7% of the general population. The presence of ER22/23EK has been associated with higher intracellular concentrations of the less active variant of the glucocorticoid receptor which may lead to glucocorticoid resistance (van Rossum, E. & van den Akker, E., 2011). Research on ER22/23EK has demonstrated more favorable metabolic profiles and body composition in carriers of the SNPs than non-carriers (Manenschijn, van den Akker, Lamberts, & van Rossum, 2009). In elderly patients, ER22/23EK has been shown to be associated with decreased risk of dementia and longevity. In younger populations, ER22/23EK has been shown to be associated with increased height (Kuningas, Mooijaart, Slagboom, Westendorp, & Heemst, 2006), as well as

increased catch-up growth and lower insulin levels in adolescents born prematurely (Finken et al., 2007).

Recent studies in adults have shown an increased risk of major depression in ER22/23EK carriers (Spijker & van Rossum, 2009). In a retrospective longitudinal adult cohort, Bet and colleagues found a moderation effect of ER22/23EK on the association of childhood adversity experienced before age 18 and depression later in life (2008). In carriers of ER22/23EK, the influence of childhood adversity increased risk of depression more than twofold (OR = 2.75, $p < .05$).

While the GR gene has been examined with respect to brain development and cognitive outcomes, a dearth of research of the rs6198 and rs6189/rs6190 SNPs and cognition exists. Further, studies of young children with respect to rs6198 and rs6189/rs6190 have been sparse or non-existent.

Cumulative Risk in Children, Stress, and Developmental Outcomes

Literature on cumulative risk in children has primarily focused upon early origins of later cognitive outcomes within childhood in addition to cross-sectional examinations of developmental outcomes within specific childhood environments. Stressing the significance of the number of risk factors in a child's background and not any single factor, Rutter studied cumulative risk in relation to psychiatric disorder in 10-year-old children (1979). Rutter's risk index included marital distress, low SES, large family size or overcrowding, paternal criminality, maternal psychiatric disorder, and admission to foster care. In this cross-sectional study, risk for psychiatric disorder rose from 2% in families with no risk factors to 20% in families with 4 or more risk factors (1979).

Another study looking at cumulative risk in relation to behavioral and emotional disorders in 11 year-old children found similar results. Using a related but different combination of risk factors, this work defined cumulative disadvantage as the number of residence and school changes, marital status, low SES, marital separation, young motherhood, low maternal cognitive ability, poor family relationships, seeking marriage counseling, and maternal depression (Williams, Anderson, McGee, & Silva, 1990). Results showed that 7% of children who had two or fewer disadvantages displayed behavioral problems in contrast to 40% of children who had eight or more. However, the study may have lacked statistical power in that the sample size was only 90 children. Further, criteria for diagnosis of emotional and behavioral disorders were vague resulting in the possibility of children with less severe disorders being misclassified and placed in the no disorder group.

Also looking at cross-sectional relationships, Evans more recently examined the association of cumulative risk and chronic physiological stress, or allostatic load, in middle school children taking into consideration the protective factor of maternal responsiveness (2007). To operationalize cumulative risk in children, the following nine domains of risk were included: crowding, noise, housing problems, family separation, family turmoil, violence, poverty, single parenthood, and maternal high school dropout. In middle school children whose mothers provided low responsiveness, higher levels of both psychosocial and physical components of the cumulative risk measure were associated with higher levels of allostatic load. The results were an expansion of Evans' earlier work which showed similar results among 8 to 10 year old children in which allostatic load was linked to higher levels of cumulative risk (Evans, Kim, Ting, Tesher, & Shannis, 2007). Unable to determine causality as in all cross-sectional studies, the major limitation of the study was the correlational design.

While research exists that reflect linkages between cumulative risk and later developmental and health outcomes, there is a dearth of evidence that specifically focuses on cognitive outcomes in high-risk samples. In one of the few studies in this realm, Sameroff and colleagues (1987) examined the association of cumulative risk in the first year of the child's life and subsequent IQ at age 4. Employing maternal, family, and demographic elements measured during the first year of the child's life, the cumulative risk index included maternal mental health, maternal anxiety, parental perspectives on child development, mother-child interaction, maternal education, head of household occupation, minority status, maternal social support, family size, and maternal stressful life events. When comparing low and high risk children from 215 families, high risk 4-year-olds were more than 24 times likely to have IQ scores below 85, or low normal intelligence. Further, no single risk factor was predictive of outcome in isolation (Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987).

Recently more studies have begun looking at the perinatal period with regards to maternal stress and cognitive outcomes but have produced variable results. In this context, cumulative risk acts an indirect proxy for biological measures of stress in addition to an indirect measure of fetal exposure to elevations in glucocorticoid levels. A number of studies have demonstrated significant associations between prenatal maternal anxiety measures and delayed cognitive and neuromotor development in children (Brouwers, van Baar, & Pop, 2001; DiPietro, Novak, Costigan, Atella, & Reusing, 2006; Davis & Sandman, 2010; Glover, O'Connor, & O'Donnell, 2010; Gutteling et al., 2006; Huizink, Robles de Medina, Mulder, Visser, & Buitelaar, 2003; Laplante et al., 2004) while others have not (Brouwers et al., 2001; Davis & Sandman, 2010; DiPietro et al., 2006).

For example, a recent study found that exposure to elevated maternal cortisol and pregnancy-specific anxiety early in human gestation (before 18 weeks) was associated with a delayed rate of development during the first year of life as well as poorer performance on measures of mental development at age 12 months (Davis & Sandman, 2010). In contrast, elevated maternal cortisol levels during late gestation (after 30 weeks) demonstrated the opposite effects, suggesting the importance of timing of cortisol exposure for infant outcomes. In late gestation, higher levels of maternal cortisol were linked to accelerated cognitive development and higher scores at 12 months (Davis & Sandman, 2010). In sum, the research demonstrates that maternal cortisol and pregnancy-specific anxiety influence fetal programming that affect later cognitive outcomes. However, the evidence may not be generalizable to high risk populations, given that Davis and Sandman's (2010) sample consisted of 112 mothers who were primarily older, nonsmoking, middle class, married women with high school degrees.

Another study by Sandman and colleagues assessed maternal psychosocial and biological stress measures, such as pregnancy-specific anxiety and cortisol, at five gestational intervals in addition to multiple points after birth through age 2 years (2011). Child neurodevelopment was examined with cognitive testing, measures of adjustment, and brain imaging between 5 and 8 years of age. Results demonstrated that psychobiological markers of stress during pregnancy result in delayed fetal maturation, disrupted emotional regulation, impaired cognitive performance during infancy, and reduced brain volume in regions associated with learning and memory in 6 to 8 year old children. In contrast to previous work, the study also demonstrated that both prenatal psychosocial and biological stress had independent, significant effects on cognitive development; elevated levels of stress hormones did not necessarily represent maternal experiences of increased psychosocial stress. With respect to reduced gray matter volume,

primary effects of high levels of prenatal maternal anxiety were seen in girls. Associations between maternal prenatal stress and brain-related deficits in children remained with the inclusion of preterm birth and growth restriction as well as a variety of postnatal controls such as postnatal maternal stress and depression. Again, Sandman and colleagues employed a healthy low risk sample of 125 subjects (Sandman et al., 2011).

Also focusing on biological measures of stress during pregnancy, Bergman and colleagues prospectively followed 125 mothers and their normally developing children from pregnancy until 17 months after birth. At approximately 17 weeks gestation, amniotic fluid was collected in order to measure fetal exposure to cortisol. Infants were assessed at 17 months using the Bayley Scales of Infant Development, and infant–mother attachment was classified using the Ainsworth Strange Situation assessment**.** The research demonstrated that prenatal cortisol exposure negatively predicted cognitive ability in infants while controlling for prenatal, obstetric, and socioeconomic factors. Further, the association was moderated by attachment status. The study is consistent with the work of Sandman's team as well as others with respect to fetal glucocorticoid exposure and unfavorable effects on cognition. Influences that lead to increased levels of stress hormones were not examined. One possible limitation of the work was that samples of amniotic fluid were only taken at one point during pregnancy, and it is possible that there could have been variation in cortisol over the course of gestation and development. As in previously described research, the study employed a fairly healthy, low risk sample (Bergman, Sarkar, Glover, & O'Connor, 2010).

Also examining maternal stress during pregnancy, recent work assessed fetal neurobehavioral development and functioning in a sample of 112 non-smoking, married, well-

educated, mature, non-Hispanic White women (DiPietro et al., 2010). Data was collected from 28 to 34 weeks gestation and in the first weeks post birth. Pregnancy-specific stress was found to be associated with higher levels of neural conductivity, fetal heart rate variability, and steeper inclines in somatic-cardiac couplings as mothers came to term, a marker for neural integration and fetal well-being (Baser, Johnson, & Paine, 1992; Johnson, Besinger, Thomas, Strobino, & Niebyl, 1992). These fetal indicators serve as proxies for neurobehavioral development in utero and led researchers to believe that neurologic maturation had been facilitated due to maternal stress (DiPietro et al., 2010).

Findings were consistent with the results found by Davis and Sandman (2010) during late gestation but run counter to other studies that demonstrate deleterious effects of maternal stress on fetal development. However, it is important to keep in mind that some level of stress is necessary for normative brain development. The authors stated that the employed stressors were more likely fall into the categories of "positive" or "tolerable" levels of stress as opposed to "toxic" levels--chronic, elevated levels that exceed the capabilities of recovery (DiPietro et al., 2010; Shonkoff, 2006). As in the Davis and Sandman study, results lacked generalizability to more diverse populations, and specifically those with fewer economic resources, exposure to multiple stress factors, and more stressful events.

In sum, research has shown that cumulative risk directly experienced by children during early childhood is associated with increased cortisol and cognitive deficit. Evidence has indicated that various social environmental stressors experienced by mothers during pregnancy and high levels of stress hormones are related to delayed cognitive development in infants. While we know that the quality of the fetal environment and the timing of exposure to a variety

of substances, including stress hormones, are critical for developmental and health outcomes (Barker, Eriksson, Forson, & Osmond, 2002; DiPietro et al., 2010; Fox & Rutter, 2010; Grossman et al., 2003), less is known about the indirect consequences of maternal cumulative risk on the fetus and later cognitive development, especially in humans (Anderson & Armstead, 1995; DiPietro et al., 2010; MacArthur Research Network on Socioeconomic Status and Health, 2009; Sameroff, Gutman, & Peck, 2003; Sandman et al., 2010). In addition, there is no consensus on how to measure cumulative risk, in general, (Evans & Kim, 2010) and empirical evidence regarding "toxic stress" and cognitive outcomes in high risk populations is lacking in perinatal research.

Present Study

Under the premise that adaptation occurs in utero that sets the course for later cognitive deficit, the current study examines the association of maternal cumulative risk, or the combined effects of chronic social and environmental stressors, during pregnancy and birth outcomes as well as IQ at ages 3 and 4 years. The impact of cumulative risk on birth outcomes provides a look at proximal, direct effects of maternal cumulative risk on the fetus. Further examining the association of maternal cumulative risk and child IQ, this work also examines possible mediation effects of birth outcomes in addition to potential moderation effects of various single nucleotide polymorphisms in the glucocorticoid receptor gene and cumulative genetic influences of reactive GR genotypes.

It is hypothesized that increased maternal cumulative risk during pregnancy will be negatively associated with birth outcomes of birth weight and gestational age. In addition, increased maternal cumulative risk during pregnancy will be negatively associated with IQ scores in children at ages 3 and 4 years. It is also hypothesized that the association of maternal cumulative risk during pregnancy and child IQ at ages 3 and 4 will remain significant after controlling for postnatal

influences of the home environment such as provision of appropriate toys, organization, variety in daily routine, safety, parenting, as well as child abuse and neglect. The change in IQ from 3 to 4 years old will also be associated with maternal cumulative risk during pregnancy. Further, the relationship between maternal cumulative risk and child IQ at ages 3 and 4 will not be highly mediated by birth outcomes, demonstrating a direct effect of maternal cumulative risk during pregnancy on cognitive development in children. Focusing on a high risk sample, the study employs a new measure of cumulative risk that accounts for pregnancy-specific and general sources of social and environmental stress.

Using a gene by environment design, this study also explores five variants of the glucocorticoid receptor (GR) gene involved in glucocorticoid sensitivity. It is the first to examine the effects of environmental maternal cumulative risk on fetal development with regards to variation in GR gene in children. It is hypothesized that variability in the GR gene will moderate the relationship between maternal cumulative risk and birth outcomes as well as child IQ at ages 3 and 4 years. Specifically, GR polymorphisms rs6190 and rs6198 in children will be associated with birthweight as well as IQ at ages 3 and 4 years. Further, GR rs6190 and rs6198 in children will moderate the relationship between maternal cumulative risk during pregnancy and child IQ at ages 3 and 4 years. As an exploratory exercise due to lack of evidence in current literature, it is hypothesized that one or more of the polymorphisms GR rs12656106, rs4244032, and/or rs2918417 in children will be associated with birthweight as well as IQ at ages 3 and 4 years. Further, GR rs12656106, rs4244032, and/or rs2918417 will moderate the relationship between maternal cumulative risk during pregnancy and child IQ at ages 3 and 4 years. Finally, the cumulative measures of genetic reactivity will also moderate the relationship between maternal cumulative risk during pregnancy and IQ at ages 3 and 4 years. These hypotheses are

in accordance with recent research that highlights the role of glucocorticoids in fetal brain development and stress pathways.

The following phenotypic research questions will be explored:

1. Is higher maternal cumulative risk during pregnancy negatively associated with birth weight?
2. Is higher maternal cumulative risk during pregnancy negatively associated with gestational age?
3. Is higher maternal cumulative risk during pregnancy negatively associated with IQ scores in children at age 3?
4. Examining the strength of the relationship between maternal cumulative risk and child IQ, is maternal cumulative risk during pregnancy still negatively associated with IQ scores in children at age 3 once controls for postnatal environment are introduced?
5. Is higher maternal cumulative risk during pregnancy negatively associated with IQ scores in children at age 4?
6. Examining the strength of the relationship between maternal cumulative risk and child IQ, is maternal cumulative risk during pregnancy still negatively associated with IQ scores in children at age 4 once controls for postnatal environment are introduced?
7. If cumulative risk is negatively associated with IQ at age 4 and gestational age or birth weight, do birth outcomes mediate the relationship between maternal cumulative risk during pregnancy and IQ in children at age 4?
8. Is maternal cumulative risk during pregnancy associated with change in IQ from age 3 to 4 years?

The following gene-environment research questions will be explored:

9. Are individual polymorphisms in the *GR* gene, such as rs6198, rs6190, rs4244032, and rs2918417, associated with birthweight?
10. Are individual polymorphisms in the *GR* gene, such as rs6198, rs6190, rs4244032, and rs2918417, associated with IQ at ages 3 and 4 years?
11. If maternal cumulative risk during pregnancy is associated with lower IQ at ages 3 and 4, do individual *GR* polymorphisms in children, such as rs4244032, rs6190, rs2918417, and rs6198, moderate these relationships?
12. If maternal cumulative risk during pregnancy is associated with lower IQ at ages 3 and 4, does a cumulative measure of genetic reactivity in the GR gene moderate these relationships?

Method

Data

Data come from the longitudinal, randomized clinical trial of the Nurse Family Partnership Program that began in Elmira, New York in 1977. In 1981, the semi-rural community was rated the worst Standard Metropolitan Statistical Area in the country in terms of economic conditions (Olds et al., 1983). The Nurse Family Partnership Program Study assessed the effects of the Nurse Family Partnership Program on pregnancy outcomes, parenting quality, child health and development, and maternal life course development.

Pregnant women were recruited through a free health department antepartum clinic, Planned Parenthood, public schools, a variety of health and human service agencies, and offices of private obstetricians. Mothers who were either unmarried, from Hollingshead social class IV or V, and/ or under age 18 at registration were actively recruited. However, in order to add to sample variability, anyone could participate regardless of age, SES, or marital status if she were nulliparous. In all, 500 women were interviewed between April 1978 and September 1980 and there were no significant differences in age, marital status, and education between those women who participated and those who declined (Olds et al., 1983).

The participants included 400 nulliparous women who were registered before their 30th week of pregnancy, or less than 26 weeks of gestation. However, for the purposes of this study, two mothers were excluded because they gave birth to twins. As a result, the full study sample included 398 mothers. Of these mothers, 61.6% were married, 60.3% were 19 years old or younger, and 45.0% had not yet graduated from high school. In addition, 88.5% were White with the remaining 11.5% characterized as “non-White”. More information on the background characteristics are presented in Tables 1 and 2.

Before treatment group assignment, women were equivalent on all standard socioeconomic background characteristics (Olds et al., 1983). Mothers were assigned at random to one of four treatment conditions. Families in treatment group one served as the original control group with no services provided to the mother during pregnancy. Children received health and developmental screenings by an infant specialist when they reached 1 or 2 years of age, as well as referrals to other specialists for further evaluation and treatment if necessary. Treatment group two consisted of families who were provided with free transportation for regular prenatal and well-child care at local clinics and physicians' offices. At one or two years of age, children received health and developmental screenings by an infant specialist. Later, treatment groups one and two were combined to form the control group due to a lack of differences between the two in use of prenatal and well-child care (Olds et al., 1986). Families in treatment group three were provided with a nurse home visitor only during pregnancy while families in treatment group 4 were provided with a nurse home visitor during pregnancy as well as the child's first 2 years of life post delivery. In addition, treatment groups three and four both received the aforementioned screenings and transportation (Olds et al., 1983).

The Elmira phenotypic data were collected at study intake, 32 weeks of pregnancy, and child birth as well as when the child was 6, 10, 12, 22, 24, 34, 36, 26, and 48 months of age. Information on family, child, and home characteristics was obtained from the study participant (mother), child, child's father, child's grandmother, pediatric and hospital medical records, and child protective service records in New York State as well as the 14 other states to which families dispersed over time. During the first 4 years after service delivery, attrition rates varied from 15 to 21% (depending on assessment period), and there were no differences across treatment groups in the proportion of participants with completed assessments (Olds et al., 1983).

When the Elmira "children" were 27 years of age, DNA was collected through blood draws, buccal swabs, and saliva (N=241). Background characteristics of the 241 mothers of children who submitted DNA samples are presented in Table 1.

Early analyses of the Elmira data demonstrated program impacts on child abuse and neglect prevention and child emergency room visit decline, especially for accidents and poisoning, for women who felt they had less control over their lives (Olds et al., 1986). There also were treatment differences in reports of maternal smoking during pregnancy, maternal social support, pre-term delivery, infant crying, positive mood, maternal conflict with and scolding of the child, and provision of appropriate play materials (Olds et al., 1986; Olds, 2002). Though marginally statistically significant, improved intellectual functioning was demonstrated in children from the highest risk families who participated in the intervention (Olds et al., 1986). Positive programs effects were concentrated in mothers who were at the highest risk for care-giving dysfunction (e.g. mothers who were unmarried, low-income, and had high external locus of control) (Olds et al., 1986). The 15-year follow-up indicated long-term effects on the number of arrests, convictions, substance abuse, and promiscuity among children of low-income, unmarried mothers who participated in the treatment group (Olds, 2002). Further, improved maternal life outcomes such as fewer subsequent pregnancies, greater workforce participation, and reduced use of public assistance, were associated with early intervention (Olds, 2002).

Measures

Maternal Cumulative Risk Index. While research on cumulative risk in children has examined life course health and development, there is no consensus as to the best means to measure cumulative risk in pregnant women with the life course of the fetus in mind. Founded on cumulative risk models presented by Sameroff and Evans, this cumulative risk index seeks to

capture environmental stressors that lead to persistent, elevated stress levels in mothers (Evans, Kim, Ting, Tesher, & Shannis, 2007; Sameroff, Seifer, Barocas, Zax, & Greenspan, 1987). The index includes both tangible life stressors (major life events that have occurred) and general life anxiety (how sources of stress are perceived) components. Requirements for index inclusion were 1) low multicollinearity among risk items (VIF = 1.19; See Table 3), 2) significant correlation between each risk item and IQ scores at ages 3 and 4) empirical basis in development, stress, and health literatures. In addition, variables were examined for normality and outliers. For each of the 12 risk factors, bivariate analyses were performed to ensure that each factor was significantly correlated with child IQ score at ages 3 and 4 (See Table 4).

Specifically, the cumulative risk index includes tangible life stress measures of maternal education (1 = high school dropout), number of individuals living in the household, maternal age (1 = 19 years old or younger), employment status (1 = unemployed), minority status (1 = non-White), marital status (1 = unmarried), and household income as stressors collected at intake. Annual household income was reported at intake in 1977 dollars and included reported income from the mother, father, and "other" sources (1 = below the 1977 federal poverty level for a family of three).

Because the models were based on Sameroff's and Evans' models in children, additional age-appropriate tangible stressors were added to reflect cumulative risk in mothers (Barker et al., 2002; Brooks-Gunn, 1991; Harburg et al., 1993; Rozanski, Blumenthal, & Kaplan, 1999; Rutter, 1979; Taylor & Repetti, 1997; Williams et al., 1990). Supplementary measures of risk assessed at 32 weeks of pregnancy include whether or not the mother had recently become homeless and been engaged in criminal behavior. The presence or absence of relationship problems at 32 weeks of pregnancy was also included (1 = emotional and/or physical abuse from a significant

other, recent marital separation/divorce, or recent marital affair). To account for possible effects of social isolation or impoverishment, the absence of a maternal support network at 32 weeks of pregnancy was also included (1 = no social support) (Cohen, Janicki-Deverts, & Miller, 2007; Collins, Dunkel-Schetter, Lobel, & Scrimshaw, 1993; Rozanski et al., 1999; Sameroff et al., 1987; Taylor & Repetti, 1997). Maternal support network was defined as having at least one individual with whom the mother reported feeling close. In addition, if participants answered "Yes", a score of 1 was also given. For example, if the mother had suffered emotional or physical abuse by her partner, she was given 1. All continuous items included in the cumulative risk index were re-coded dichotomously. For example, the number of individuals living in the household in the top quartile of the sample distribution was given a score of 1. A score of 0 was given to all other cases.

The inclusion of a general life anxiety component was another augmentation based on existing stress literature targeted to an adult population (Cohen et al., 2007; Kivimaki et al., 2006; MacArthur Research Network on Socioeconomic Status and Health, 2009; Melamed, 1995; Rozanski et al., 1999; Taylor & Repetti, 1997). General life anxiety was measured by a survey administered at 32 weeks of pregnancy that included questions regarding general anxiety about employment and/or school; living arrangements; finances; upsetting others due to pregnancy; caring for the baby once born; attributes and health of the baby; emotions, dependence, and appearance during pregnancy; giving birth; and own health (Olds et al., 1983). All general life anxiety items were evaluated using Likert scales that ranged from 1 to 5 (1 = "Not worried at all"; 5 = "Extremely worried"). The 9 items were summed to create measure that ranged from 0 to 45, and the Cronebach's α for the scale was 0.81. The general life anxiety

component was re-coded dichotomously with a score of 1 given if the mother's exposure was in the top quartile of the sample distribution.

Cumulative risk exposure (0-12) was calculated by summing across the 12 singular risk factors. The index was then used as a continuous measure to preserve power. The range of scores among the full sample of mothers was 1 to 9 with a mean of 4.2 and standard deviation of 2.1. In the sample of mothers whose children later provided DNA at age 27 years, the range of scores for cumulative risk exposure was 1 to 9 with a mean of 4.3 and standard deviation of 2.0.

Birth outcomes. Birthweight and gestational age have been found to predict IQ up to 18 years later. For example, research has shown that 8-month-old infants with lower birth weight and higher neonatal risk scores are at higher risk of neurological impairment and perform worse on measures of verbal IQ at age 8 years as compared to their peers with normal head sizes (Hack et al., 1991). Although the strength of association declines with age, heavier birth weight and better neonatal health have been positively associated with cognitive outcomes at 12, 24, and 36 months of age (Brooks-Gunn, Klebanov, Liaw, & Spiker, 1993). In a high risk sample, very low birth weight was associated with lower IQ scores even at school age (McCormick, Brooks-Gunn, Workman-Daniels, Turner, & Peckham, 1992). Infants who were born under 750 g performed worse than other infants on measures of psychomotor skills, cognitive ability, and academic achievement in kindergarten. In addition, gestational age was significantly associated with IQ in children who had very low birth weight (Hack et al., 1994). More recent work by Hack and colleagues (2002) has demonstrated that adolescents who were born under 1500 g had a lower mean IQ, had poorer academic achievement, and were less likely to graduate high school than their normal birth weight peers. Gestational age has also been shown to be important with regard

to brain structure and function. Research has shown that babies born at 33 weeks or less have lower IQ scores in adolescence relative to their full term counterparts (Narberhaus et al., 2007).

In this study, birthweight (in grams) was obtained from hospital records while gestational age was estimated by local pediatricians and nurse practitioners who conducted physical exams and a modified Dubowitz Gestational Age Assessment (Dubowitz, Dubowitz, & Goldberg, 1970). In addition, the estimated length of gestation was based upon the mother's last reported menstrual period and ultrasound readings taken at less than 28 weeks of gestation for some women. Both birth outcomes were employed as continuous variables in the analysis (See Table 2).

IQ at ages 3 and 4 years. In the Western world, IQ is often seen to be a predictive measure of education and career progression and performance (Sternberg, Grigorenko, & Bundy, 2001). There is evidence that supports a negative relationship between IQ and delinquency, independent of social class, race, and gender. Despite normative variations, IQ is fairly stable during development within individuals (Sternberg et al., 2001). In addition, the predictability of IQ increases with child's age (Sternberg et al., 2001).

At ages 3 and 4 years, children's IQ was assessed using the Stanford-Binet Form L-M Test of Intelligence, the most commonly used intelligence test for this age group (Sattler, 1992). The Stanford-Binet measure of IQ has been shown to be fairly stable from age 3 to 12 years (Sternberg et al., 2001). Normed for the 1973 population of American children, the L-M version of the test included vocabulary measures and a single age scale in order to assess general intelligence. Form L-M maintains approximately a 0.80 correlation with current general intelligence components of new versions of the Stanford-Binet (Becker, 2003). In this analysis, the Stanford-Binet Intelligence test was employed as a continuous variable. At age 3 years, the

range of IQ scores was 61.0 to 160.0 with a mean of 102.8 and standard deviation of 14.6 points. At age 4 years, the range of scores was 68.0 to 160.0 with a mean of 109.6 and standard deviation of 13.8 (See Table 2).

Maternal controls. Because poor nutritional status is a form of prenatal stress that can modify HPA axis function as well as birth outcome, the maternal Nutrient Adequacy Reporting Survey (NARS) reported at 32 weeks of pregnancy was included (Cohen et al., 2007; Desai & Hales, 1997; Kapoor et al., 2006; Seckl & Holmes, 2007; Welberg & Seckl, 2001). Maternal smoking status at intake, measured as the number of cigarettes smoked per day, was also included due to its association with impaired intellectual functioning in the first four years of life, among other adverse child outcomes (Olds, Henderson, & Tatelbaum, 1994). Treatment group was also included as a control variable with participation in the Nurse Family Partnership Program coded as 1. Maternal smoking and NARS were included as continuous variables (See Table 1).

Child controls. Child sex was included as a control variable to account for any possible sex differences in birth outcome as well as HPA axis stress response (Kudielka & Kirschbaum, 2005; Muller & Bale, 2008; Seckl & Holmes, 2007; Willerman, 1972) (See Table 2).

Postnatal environment. In order to take into account the effects of both intra and extra-uterine environments on cognitive development, the quality of the child's home environment was assessed using Caldwell's Early Childhood Home Observation for Measurement of the Environment (EC-HOME) at ages 3 and 4 years (Bradley & Caldwell, 1980; Caldwell & Bradley, 1979; Totsika & Sylva, 2004). Based on direct observations of the home environment and semi-structured interviews with mothers, this 55-item measure assessed provision of appropriate play materials, organization, and variety in daily routine, as well as the safety of the

home environment with respect to home hazards and poisons. It also examined maternal involvement, emotional and verbal responsiveness, and avoidance of restriction and punishment. The internal consistency for this version is 0.93 (Bradley & Caldwell, 1979) (See Table 2).

The number of incidences of child abuse and neglect from birth until age 4 years were also included in the model, when applicable. Extracted from the records of the county child-protective services unit, only reports of verified cases of neglect or abuse as defined by New York State law were included. Further, records were examined from state central registries from 15 other states to which families dispersed until the child was age 4 years (See Table 2).

Genetic markers. DNA was extracted from samples collected via 5 mL vacutainer tubes containing ethylenediaminetetraacetic acid (EDTA). Genomic DNA was then sent to Illumina for genotyping where it was immobilized in streptvidin-coated magnetic beads. Assay oligonucleotides were then annealed to genomic DNA, and oligo extension and ligation occurred. PCR amplification took place before hybridization and imaging using a BeadArray reader (Fan et al., 2003). The glucocorticoid gene was sampled multiple times to account for multiple markers and haplotypes (blocks of combinations of SNPs within one gene). SNPs were selected due to the following criteria: 1) empirical evidence of association with glucocorticoid sensitivity, 2) SNPs adequately represented the glucocorticoid receptor gene, and 3) availability of markers. SNPS from the glucocorticoid receptor (GR) gene included rs12656106, rs4244032, rs6190, rs2918417, and rs6198. Table 2 presents the SNPs examined in this study and the distribution of genotype frequencies. For the five SNPs, missing data ranged from 1.2 to 2.0% and were not imputed. All SNPs are located on chromosome 5 (5q31-32) (NCBI, 2010) (See Figure 1). No samples failed genotyping consistently.

As a check of data quality and error in genotyping, Hardy-Weinberg Equilibrium (HWE) Testing was performed using Haploview. Errors have been shown to lead to false homozygotes and a heterozygote deficiency (Ziegler & Konig, 2010). HWE assumes that genotype and genotype frequencies remain stable over generations in a large, randomly mating sample. It also assumes that there is a fixed relationship between allele and genotype frequencies (Ziegler & Konig, 2010). Four out of five SNPs were in HWE; these included rs6198, rs6190, rs2918417, and rs4244032. Glucocorticoid receptor rs12656106 deviated from HWE and was not included in analyses.

To examine the association of GR alleles at given loci, linkage disequilibrium was examined using Haploview as well (See Figure 2). For the remaining markers, linkage disequilibrium (LD) proved fairly low for all markers with R^2 ranging from 0.03 to 0.38. LD of 0.8 and higher typically indicates high correlation (Ziegler & Konig, 2010). Low LD indicated that each SNP employed in this analysis investigated a different section of the genome.

All SNPs were coded in three different ways. First, to examine "per allele" risk, each SNP was coded with the homozygous genotype composed of the highest frequency alleles as 0, heterozygous genotype as 1, and the homozygous genotype made of the lowest frequency alleles as 2. Next, SNPs were coded dichotomously to examine risk of minor versus major alleles. Again, the homozygous genotype made of the highest frequency alleles was designated as 0. The remaining combination of hetero and homozygous genotypes were coded as 1. Finally, to delve deeper, individual genotypes within a given SNP were dummy-coded. For example, genotype A/A of rs6198 was coded as 1 with A/G and G/G coded as 0. In a different variable characterizing rs6198, genotype A/G was coded as 1 with A/A and G/G coded as 0. In yet another variable describing rs6198, genotype G/G was coded as 1 with A/A and A/G coded as 0.

Cumulative Genetic Risk. An additive measure of genetic risk was created by coding reactive alleles that inferred risk as 1 and those that had no significant or served as a protective factor as 0. Cumulative genetic risk exposure in children (0-2) was calculated by summing across the 2 reactive genetic risk factors—rs6190 G and rs6198 G (See Table 2).

Analytic Strategy

Data were analyzed using STATA versions 10 and 11. To increase power, issues of missing data were remedied using multiple imputation chained equations (ICE in STATA) (UCLA: Academic Technology Services, Statistical Consulting Group, 2010) for all independent variables. Multiple imputation methods were not employed for genetic data and dependent variables of interest. Running appropriate regression models (e.g. linear, logistic, or multinomial regression) depending on data type, this multiple imputation strategy uses all other variables in the model as predictors of a single variable of interest that contains missing data. Analyses of models of interest are run in each of the imputed data sets and later combined to produce a single set of results.

Containing different sets of imputed variables, five imputed datasets were created to fit the multiple regression models. In single imputation methods, imputations are only estimates and tend to overstate confidence in parameter estimates. Multiple imputations allows for the uncertainty in the imputed values to be taken into account. Five imputed datasets were employed due to the small amount of missing data in this study (UCLA: Academic Technology Services, Statistical Consulting Group, 2010). It is important to note that only models examining phenotypic data employed imputed data.

To explore research questions 1, 2, 3, and 5, multiple regressions were employed to test the association between maternal cumulative risk during pregnancy and birth weight, gestational age, and child IQ scores at ages 3 and 4 years while controlling for various maternal and child characteristics. With regards to research questions 4 and 6, tests for robustness of the association between maternal cumulative risk and child IQ at ages 3 and 4 were also performed. Here, measures of home environment quality when children were 3 and 4 years old were added to previous models. Reports of child abuse from birth to age 4 are also added to the model that included IQ at 4 years to further examine the strength of the association between maternal cumulative risk and IQ at age 4 years. If the association proves significant, the analyses will demonstrate the direct association of maternal cumulative risk during pregnancy with cognitive deficit in early childhood after accounting for exposure to the extra-uterine environment.

If maternal cumulative risk is associated with child IQ at 4 years and gestational age or birthweight, mediation effects of birth outcomes will be assessed using multiple regression and the Sobel-Goodman test of mediation in STATA to address research question 7 (UCLA: Academic Technology Services, Statistical Consulting Group, 2010). With regards to research question 8, a paired t-test will be employed first to determine if mean IQ scores at ages 3 and 4 differed. Once a significant difference in scores is established, a Multivariate Analysis of Variance (MANOVA) will be used to determine if maternal cumulative risk during pregnancy is associated with change in IQ from age 3 to 4 years.

The overall objective of the gene analyses was to examine whether there were individual effects of polymorphisms in the GR gene that moderate the association of maternal cumulative risk and IQ at ages 3 and 4. To examine gene-environment hypotheses (research questions 9 and 10), a distribution of 4 genetic variants in the *GR* gene were investigated using stepwise multiple

regressions. Further, to address research question 11, multiple regression models with single SNP analyses were employed to examine two way interactions between maternal cumulative risk during pregnancy and various genotypes. Linear combinations of estimators (lincom in STATA 11.0) were then performed to compare the effects of maternal cumulative risk during pregnancy on IQ at ages 3 and 4 in the presence of specific genotypes within functional SNPs. Finally, multiple regression was used to assess interaction effects of cumulative genetic reactivity in the GR gene on the association of maternal cumulative risk during pregnancy and IQ at ages 3 and 4.

Sensitivity Checks

For the phenotypic portion of this study, analyses were conducted in the full sample of 398 subjects to make use of the larger sample size. Due to attrition, DNA was only collected for 241 of the children born to mothers in the original cohort. Genetic analyses were accomplished using a restricted sample. Therefore, several analyses were conducted in both the full and restricted samples to ensure comparability.

In general, results were very similar in both the full sample and sample in which DNA was collected from children at age 27 years. The largest difference was that maternal cumulative risk was associated with gestational age in the full sample but not the restricted sample. After controlling for maternal and child characteristics, infants were born 0.17 weeks earlier ($p<.05$) per one unit increase in cumulative risk during pregnancy in the full sample (See Table 9). As demonstrated by the R^2, 2.0% of the variation in gestational age was predicted by maternal cumulative risk during pregnancy.

Increased maternal cumulative risk during pregnancy was significantly associated with lower birth weight in both the full sample as well as the sample in which DNA was collected. After controlling for maternal and child characteristics, infants were born 47.49 grams lighter

($p<.01$) per one unit increase in maternal cumulative risk during pregnancy in the full sample (See Table 9). In the restricted sample for which DNA was collected, infants were born 47.17 grams lighter ($p<.01$) per one unit increase in maternal cumulative risk during pregnancy. As demonstrated by the R^2, 6.0% of the variation in birth weight in the full sample and 7.0% in the restricted sample was predicted by maternal cumulative risk during pregnancy (See Table 9).

Increased maternal cumulative risk during pregnancy was significantly associated with lower IQ scores in children at age 3 years in both the full sample as well as the sample in which DNA was collected. Controlling for maternal and child characteristics, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.56 points in IQ at age 3 years ($p\leq0.001$) in the full sample (See Table 10, Model 1). In the restricted sample for which DNA was collected, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.61 points in IQ at age 3 years ($p\leq0.001$) (See Table 11, Model 1). As reported by the R^2, 7.0% of the variation in child IQ at 3 years was predicted by maternal cumulative risk during pregnancy in both the full and restricted samples while controlling for treatment group, maternal smoking, maternal nutrition, and child sex.

Increased maternal cumulative risk during pregnancy was significantly associated with lower IQ scores in children at age 3 when postnatal home environment was included in both the full sample as well as the sample in which DNA was collected. Controlling for maternal and child characteristics, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.02 points in IQ at age 3 years ($p\leq0.01$) in the full sample when postnatal controls were added (See Table 10, Model 2). In the restricted sample for which DNA was collected, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.06 points in IQ at age 3 years ($p\leq0.05$) (See Table 11, Model 2). As reported by

the R^2, 17.0% of the variation in child IQ at 3 years was predicted by maternal cumulative risk during pregnancy in the full sample and 21.0% in the restricted sample while controlling for treatment group, maternal smoking, maternal nutrition, and child sex.

Increased maternal cumulative risk during pregnancy was significantly associated with lower IQ scores in children at age 4 in both the full sample as well as the sample in which DNA was collected. Controlling for maternal and child characteristics, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.93 points in IQ at age 4 years ($p \leq 0.001$) in the full sample (See Table 12, Model 1). In the restricted sample for which DNA was collected, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.98 points in IQ at age 4 years ($p \leq 0.001$) (See Table 13, Model 1). As reported by the R^2, 12.0% of the variation in child IQ at 4 years was predicted by maternal cumulative risk during pregnancy in the full sample and 11.0% in the restricted sample while controlling for treatment group, maternal smoking, maternal nutrition, and child sex.

When measures of the postnatal environment were added to the model, maternal cumulative risk during pregnancy was still significantly associated with IQ scores in children at age 4 in both the full sample as well as the sample in which DNA was collected. Specifically, when reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were added to the model, 4 year-old children scored 1.01 points lower on IQ for each one unit increase in cumulative risk ($p \leq 0.01$) in the full sample (See Table 12, Model 2). In the restricted sample, 4 year-old children scored 1.14 points lower on IQ for each one unit increase in cumulative risk ($p \leq 0.01$) (See Table 13, Model 2). As indicated by the R^2, 26.0% of the variation in child IQ at 4 years was predicted by maternal cumulative risk during pregnancy in the full and restricted

samples while accounting for treatment group, maternal smoking, maternal nutrition, child sex, as well as the aforementioned postnatal controls.

Results: Maternal Cumulative Risk and IQ

For ease in comparison and discussion, the following results sections will detail analyses performed in the restricted DNA sample.

Birth weight. Increased maternal cumulative risk during pregnancy was negatively associated with birth weight. After controlling for maternal and child characteristics, infants were born 58.99 grams lighter ($p<.01$) per one unit increase in maternal cumulative risk during pregnancy (See Table 17, Model 1). As demonstrated by the R^2, 8.0% of the variation in birth weight was predicted by maternal cumulative risk during pregnancy.

Gestational age. Maternal cumulative risk during pregnancy was not associated with gestational age.

IQ at age 3. Increased maternal cumulative risk during pregnancy was negatively associated with IQ scores in children at age 3 years. Controlling for maternal and child characteristics, an increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 1.76 points in IQ at age 3 years ($p\leq0.001$) (See Table 18, Model 1). As reported by the R^2, 9.0% of the variation in child IQ at 3 years was predicted by maternal cumulative risk while controlling for treatment group, maternal smoking, maternal nutrition, and child sex.

IQ at age 3 with postnatal controls. Increased maternal cumulative risk during pregnancy was negatively associated with IQ scores in children at age 3 when postnatal home environment was included. When postnatal controls were added, an increase of 1 unit in maternal cumulative risk during pregnancy was associated with a decrease of 0.82 points in IQ at age 3 years ($p\leq0.05$) (See Table 18, Model 2). As reported by the R^2, 24.0% of the variation in child IQ at 3 years was predicted by maternal cumulative risk during pregnancy while controlling for treatment group, maternal smoking, maternal nutrition, child sex, and home environment.

IQ at age 4. Increased maternal cumulative risk during pregnancy was negatively associated with IQ scores in children at age 4. Controlling for maternal and child characteristics, an increase of 1 unit in maternal cumulative risk during pregnancy was associated with a decrease of 2.62 points in IQ at age 4 years ($p \leq 0.001$) (See Table 21, Model 1). As reported by the R^2, 14.0% of the variation in child IQ at 4 years was predicted by maternal cumulative risk while controlling for treatment group, maternal smoking, maternal nutrition, and child sex.

IQ at age 4 with postnatal controls. When measures of the postnatal environment were added to the model, maternal cumulative risk during pregnancy was still negatively associated with IQ scores in children at age 4. Specifically, when reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were added to the model, children scored 1.30 points lower on IQ for each one unit increase in cumulative risk ($p \leq 0.05$) (See Table 21, Model 2). As indicated by the R^2, 36.0% of the variation in child IQ at 4 years was predicted by maternal cumulative risk during pregnancy. For an additional test of robustness, birth weight was added as a control, proved not to be significant, and had no impact on the strength of association between maternal cumulative risk during pregnancy and IQ at age 4 (See Table 14).

Mediation of birth outcomes. Because maternal cumulative risk was associated with birth outcomes as well as IQ at ages 3 and 4, a test of mediation was performed. The Sobel-Goodman test of mediation demonstrated that the mediation effect of low birth weight on IQ at ages 3 and 4 was significant, but small. At age 3, low birth weight explained 8.9% of the total effect of maternal cumulative risk during pregnancy on Stanford-Binet scores ($p \leq .001$). At age 4, low birth weight explained 8.2% of the total effect of maternal cumulative risk during pregnancy on Stanford-Binet scores ($p \leq .001$). There was no mediation effect of gestational age

with respect to the association of maternal cumulative risk during pregnancy and IQ at 3 and 4 years of age.

Change in IQ from ages 3 to 4. Maternal cumulative risk during pregnancy is associated with change in IQ from age 3 to 4 years. There was a significant difference in IQ from age 3 to 4 years (t (206) = 12.40, $p < .001$). Further, maternal cumulative risk during pregnancy was associated with change in IQ from 3 to 4 years (F (2, 135) = 6.48, $p < .01$) (See Tables 15 and 16). However, the Wilks' lambda indicated that 93.6 percent of the variance in IQ change could not be explained by maternal cumulative risk during pregnancy alone.

Discussion: Maternal Cumulative Risk and IQ

Consistent with prior literature, the current study examines the cumulative effects of chronic environmental stressors that contribute to increased levels of maternal stress hormones during pregnancy and poor cognitive outcomes in young children. While it is well-known that birth outcomes reflect genetic predisposition and adaptation to exposures that influence the structure and function of physiological systems within the developing fetus, less is known about the consequences of fetal exposures to maternal stress on postnatal cognitive outcomes independent of birth outcomes (Davis & Sandman, 2010). In contrast to singular components, past work has demonstrated that it is the cumulative effects from multiple risk factors during early childhood that increase the risk that development will be compromised (Evans et al., 2007; Rutter, 1979; Sameroff et al., 1987). Further, more risk factors are associated with poorer cognitive outcomes (Klebanov & Brooks-Gunn, 2006; Sameroff et al., 1987). Using a measure that seeks to capture multiple environmental stressors that lead to persistent, elevated stress levels in mothers during pregnancy, the current study extends this literature by demonstrating that increased levels of maternal cumulative risk are negatively associated with IQ scores in children at ages 3 and 4.

As previously mentioned, birth outcomes are traditionally viewed as proxies for the intrauterine environment with growth retardation often acting as a protective mechanism for survival (Seckl, Drake, & Holmes, 2005). Maternal cumulative risk during pregnancy was not associated with gestational age. However, it is possible that this relationship exists but was difficult to detect due to sample size. In the full sample of 398 mothers, an increase in maternal cumulative risk was associated with a decrease in gestational age. However, this association did not hold true in the restricted sample that is the focus here. In addition, the measure employed for gestational age in this

study was based on a modified Dubowitz Gestational Age Assessment for some participants and an estimate of length of gestation based upon last reported menstrual period and ultrasound readings taken at less than 28 weeks of gestation for others. Therefore, the measure itself may not have internal consistency.

Increases in maternal cumulative risk during pregnancy were negatively associated with birth weight. Thus, we can conclude that cumulative risk did affect the intrauterine environment with impact on the developing fetus. However, tests of mediation showed that the effects of birth weight only partially mediated the relationship between maternal cumulative risk during pregnancy and IQ scores in preschoolers to a small extent, while gestational age had no mediation effect. Cumulative risk during pregnancy therefore had a direct relationship with IQ. Maternal cumulative risk during pregnancy was also negatively associated with IQ scores in children at ages 3 and 4 when accounting for some aspects of the postnatal environment. These results add strength to the assertion that maternal cumulative risk during pregnancy is one common factor that gives rise to both poor birth outcomes and fetal programming for later developmental and physiological deficits.

To put findings in a broader context, lead exposure studies in disadvantaged populations of school-age children demonstrate an estimated loss of 1.85 IQ points (+/- 0.92) per 10 to 20 μg/dl increase in lead (Schwartz, 1994). Impacts of lead poisoning in children have lead to action at the federal level through the Centers for Disease Control and Prevention's Childhood Lead Poisoning Prevention. Underscoring the importance of the detrimental, yet preventable, impacts of lead in children, the reduction of elevated blood levels in children is an objective in Healthy People 2020, the Nation's roadmap for improving the health of all Americans (U.S. Department of Health and Human Services, 2011). The current study demonstrates cognitive impacts similar to that of lead positioning in children---the effects of maternal cumulative risk

exposure during pregnancy on IQ at age 4 are comparable with an estimated loss of 1.98 IQ points (+/-0.45).

Results: Maternal Cumulative Risk and IQ with Genetic Moderation

Birth weight: GR rs6198, rs6190, rs4244032, and rs2918417. Without controlling for genetic effects, infants were born 58.99 grams lighter ($p<.01$) per one unit increase in maternal cumulative risk. As indicated by the R^2, 8.0% of the variation in birthweight was predicted by maternal cumulative risk during pregnancy (See Table 17, Model 1).

When genetic effects were added to the model, individual polymorphisms in the *GR* gene, rs6198, rs6190, rs4244032, and rs2918417, were not associated with birth weight. Further, the inclusion of rs6190, rs4244032, and rs2918417 did not explain any additional variance (See Table 18). The only exception was GR rs6198.

When rs6198 (A/G and G/G) was included with controls, infants were born 51.84 grams lighter ($p<.01$) per one unit increase in maternal cumulative risk during pregnancy (See Table 17, Model 4). As indicated by the R^2, 9.0% of the variation in birthweight was predicted by maternal cumulative risk during pregnancy when accounting for rs6198.

IQ at ages 3 and 4: GR rs4244032 and rs2918417. The polymorphisms, rs4244032 and/or rs2918417, in the GR gene in children were not associated with child IQ at ages 3 and 4 years and did not considerably alter the effects of maternal cumulative risk on IQ when controlled for. The polymorphisms, rs4244032 and/or rs2918417, in the *GR* gene in children did not moderate the relationship between maternal cumulative risk during pregnancy and child IQ at age 3 and 4 years.

IQ at ages 3 and 4: GR rs6198. Controlling for maternal and child characteristics, an increase of 1 point in maternal cumulative risk during pregnancy was associated with a decrease of 1.79 points in IQ at age 3 years ($p\leq0.01$) when accounting for rs6198 (A/G and G/G) (See Table 18, Model 3). However, this trend was similar when rs6198 (A/G and G/G) was not

included in the model (See Table 18, Model 1) As indicated by the R^2, 9.0% of the variation in IQ at age 3 years was predicted by maternal cumulative risk during pregnancy when accounting for rs6198.

When postnatal controls were introduced, the association between maternal cumulative risk and IQ at 3 years was no longer significant (See Table 18, Model 4). Again, this trend was similar in models when rs6198 (A/G and G/G) were not included (See Table 18, Model 2). As indicated by the R^2, 24.0% of the variation in IQ at age 3 years was predicted by maternal cumulative risk during pregnancy when accounting for minor alleles of rs6198 and postnatal home environment. The association between maternal cumulative risk and IQ at age 3 years was also not significant with the inclusion of interaction terms in models with and without postnatal home environment (See Table 19, Models 1 and 2). Further, there was no interaction effect of rs6198 (A/G and G/G) and maternal cumulative risk.

However, examining the graph of these interactions, it appeared as if there was some type of interaction effect (See Figure 3). When the relationship of maternal cumulative risk during pregnancy and IQ at age 3 was examined in the two allelic conditions, the effect of maternal cumulative risk on IQ at 3 years was significant when rs6198 (A/G and G/G) was present. An increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 3.11 points in IQ at age 3 years ($p \leq 0.001$) in the presence of rs6198 (A/G and G/G) in contrast to no association when A/A was present (See Table 20).

It is also important to note that when rs6198 was defined by per allele risk, the association between maternal cumulative risk and IQ at age 3 years was not significant. Further, when A/G and G/G genotypes were added to the model individually, the association between maternal cumulative risk and IQ at age 3 years was not significant.

Controlling for maternal and child characteristics, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 2.60 points in IQ at age 4 years ($p \leq 0.001$) when accounting for the per allele risk of rs6198 (See Table 21, Model 3). However, this trend was similar when per allele risk of rs6198 was not accounted for in the model (See Table 21, Model 1). As indicated by the R^2, 14.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for the per allele risk of rs6198.

When postnatal controls of reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were added to the model, the association between maternal cumulative risk and IQ at 4 years remained significant; an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.32 points in IQ at age 4 years ($p \leq 0.05$) when accounting for the per allele risk of rs6198 (See Table 21, Model 4). However, this trend was similar in models without the inclusion of per allele risk of rs6198 (See Table 21, Model 2). As indicated by the R^2, 36.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6198 and postnatal home environment. Interaction effects of per allele risk in rs6198 and maternal cumulative risk were significant without and with postnatal controls included ($p \leq 0.05$, $p \leq 0.01$, respectively) (See Table 22, Models 1 and 2, and Figure 4). As indicated by the R^2, 18.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6198 and interaction terms. When postnatal controls were added to this model, 39.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy.

The association between maternal cumulative risk during pregnancy and IQ at age 4 years was also not significant with the inclusion rs6198 (A/G and G/G) without and with postnatal controls. However, the interaction of rs6198 (A/G and G/G) and maternal cumulative risk was significant without and with postnatal controls ($p \leq 0.05$) (See Table 23, Models 1 and 2, and Figure 5). As indicated by the R^2, 18.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for rs6198 (A/G and G/G) and interaction terms. As indicated by the R^2, 39.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for rs6198 (A/G and G/G), interaction terms, and postnatal controls. When G/G and A/G genotypes were run separately, there was no association between maternal cumulative risk during pregnancy and IQ at age 4 years with and without postnatal controls and no effects of moderation. When the rs6198 A/A genotype and interaction terms for allelic and maternal cumulative risk were included, interaction effects were significant without and with postnatal controls ($p \leq 0.05$). (See Table 23, Models 3 and 4, and Figure 5). As indicated by the R^2, 18.0 % of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for rs6198 A/A and interaction terms. When postnatal controls were added to the model, 39.0% of the variation in IQ at age 4 was predicted by maternal cumulative risk during pregnancy.

When the relationship of maternal cumulative risk during pregnancy and IQ at age 4 was examined in the two allelic conditions, the effect of maternal cumulative risk on IQ at 4 years was significant when rs6198 (A/G and G/G) was present. An increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 5.08 points in IQ at age 4 years ($p \leq 0.001$) in the presence of the combination of rs6198 genotypes A/G and G/G and a decrease

of 1.89 points in IQ at age 4 years ($p \leq 0.01$) in the presence of rs6198 genotype A/A (See Table 24).

IQ at ages 3 and 4: GR rs6190. Controlling for maternal and child characteristics, an increase of 1 point in maternal cumulative risk during pregnancy was associated with a decrease of 1.85 points in IQ at age 3 years ($p \leq 0.01$) when accounting for the per allele risk of rs6190 (See Table 25, Model 3). When postnatal controls were added to the model, the association between maternal cumulative risk and IQ at 3 years was no longer significant (See Table 25, Model 4). This trend was similar in models that did not control for the per allele risk of rs6190 (See Table 25, Models 1 and 2). As indicated by the R^2, 8.0 % of the variation in IQ at age 3 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6190. When postnatal controls were added to the model, 25.0% of the variation in IQ at age 3 was predicted by maternal cumulative risk during pregnancy.

Controlling for maternal and child characteristics, an increase of 1 unit in maternal cumulative risk during pregnancy was associated with a decrease of 2.06 points in IQ at age 3 years ($p \leq 0.001$) when accounting for the per allele risk of rs6190 and the interaction effects of maternal cumulative risk and per allele risk of rs6190 (See Table 26, Model 1). Here, there were no significant interaction effects. When postnatal home environment was added, again, the association between maternal cumulative risk during pregnancy and IQ at 3 years was no longer significant (See Table 26, Model 2). As indicated by the R^2, 13.0 % of the variation in IQ at age 3 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6190 and interaction effects. When postnatal controls were added to the model, 26.0% of the variation in IQ at age 3 was predicted by maternal cumulative risk during pregnancy.

Digging deeper, an increase of 1 point in maternal cumulative risk during pregnancy was associated with a decrease of 1.86 points in IQ at age 3 years ($p \leq 0.01$) when accounting for rs6190 (A/G and A/A), decrease of 1.95 points in IQ at age 3 ($p \leq 0.001$) when accounting for rs6190 A/G and rs6190 A/A, decrease of 1.91 points in IQ at age 3 ($p \leq 0.001$) when accounting for rs6190 G/G, decrease of 2.03 points in IQ at age 3 ($p \leq 0.001$) when accounting for the interaction of rs6190 (A/G and A/A) and maternal cumulative risk during pregnancy (See Table 27). When rs6190 A/G and A/A genotypes were run separately, there was no association between maternal cumulative risk and IQ at age 3 years. When postnatal home environment was added, the association between maternal cumulative risk and IQ at 3 years was no longer significant. There were no interaction effects with and without postnatal controls.

However, examining the graph of these interactions, it appeared as if there was some type of interaction effect (See Figure 6). When the relationship of maternal cumulative risk during pregnancy and IQ at age 3 was examined in the two allelic conditions, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 2.03 points in IQ at age 3 years ($p \leq 0.001$) in the presence of rs6198 G/G in contrast to no association when rs6190 (A/G and A/A) was present (See Table 28).

Controlling for maternal and child characteristics, an increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 2.56 points in IQ at age 4 years ($p \leq 0.001$) when accounting for the per allele risk of rs6190 (See Table 29, Model 3). However, this trend was similar when per allele risk of rs6190 was not included in the model (See Table 29, Model 1). As indicated by the R^2, 17.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for the per allele risk of rs6190.

When postnatal controls of reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were added to the model, the association between maternal cumulative risk and IQ at 4 years remained significant. This trend was similar in models where per allele risk of rs6190 was not included (See Table 29, Model 2). Controlling for maternal and child characteristics as well as postnatal environment, an increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 1.31 points in IQ at age 4 years ($p \leq 0.05$) when accounting for the per allele risk of rs6190 (See Table 29, Model 4). As indicated by the R^2, 36.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6190 and postnatal environment.

When adding interaction terms of per allele risk of rs6190 and maternal cumulative risk, an increase of 1 unit in maternal cumulative risk during pregnancy was associated with a decrease of 2.84 points in IQ at age 4 years ($p \leq 0.001$) (See Table 30, Model 1). There were no interaction effects. As indicated by the R^2, 19.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6190 and interaction terms.

When postnatal controls of reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were added to this model, the association between maternal cumulative risk and IQ at 4 years remained significant (See Table 30, Model 2). In this model, per allele risk of rs6190 and the interaction effects proved significant, as well. As indicated by the R^2, 38.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for per allele risk of rs6190, interaction terms, and postnatal environment.

Digging deeper, an increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 2.87 points in IQ at age 4 years ($p \leq 0.001$) when accounting for interaction

effects of rs6190 (A/G and A/A) and maternal cumulative risk (See Table 31, Model 1). However, there were no interaction effects. As indicated by the R^2, 19.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when controlling for rs6190 (A/G and A/A) and interaction terms. When postnatal environment was added, the association between maternal cumulative risk and IQ at 4 years remained significant. Here, there were interaction effects between maternal cumulative risk during pregnancy and rs6190 (A/G and A/A) ($p \leq 0.01$) (See Table 31, Model 2). As indicated by the R^2, 40.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for postnatal environment, rs6190 (A/G and A/A), and interaction terms.

An increase of 1 point in cumulative risk during pregnancy was associated with a decrease of 2.92 points in IQ at age 4 years ($p \leq 0.001$) when accounting for interaction effects of rs6190 A/G and maternal cumulative risk (See Table 31, Model 3). However, there were no interaction effects. As indicated by the R^2, 19.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when controlling for rs6190 A/G and interaction terms. When postnatal environment was added, the association between maternal cumulative risk and IQ at 4 years remained significant. Here, there were interaction effects between maternal cumulative risk during pregnancy and rs6190 A/G ($p \leq 0.001$) (See Table 31, Model 4). As indicated by the R^2, 42.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for postnatal environment, rs6190 A/G, and interaction terms.

An increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 2.62 points in IQ at age 4 years ($p \leq 0.001$) when accounting for rs6190 G/G (See Table 32, Model 1). When postnatal environment was added, the association between maternal cumulative

risk and IQ at 4 years remained significant. An increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 1.32 points in IQ at age 4 years ($p \leq 0.05$) when accounting for rs6190 G/G and postnatal controls (See Table 32, Model 2).

There were no interaction effects without postnatal controls (See Table 32, Model 3). However, when postnatal controls were included, there was an interaction effect of rs6190 G/G on the association of maternal cumulative risk during pregnancy and IQ at 4 years ($p \leq 0.01$) (See Table 32, Model 4). As indicated by the R^2, 19.0% of the variation in IQ at age 4 was predicted by maternal cumulative risk during pregnancy when controlling for rs6190 G/G and interaction terms. As indicated by the R^2, 40.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for postnatal environment, rs6190 G/G, and interaction terms. It is also important to note that rs6190 A/A had no significant impact on the association of maternal cumulative risk during pregnancy and IQ at age 4.

Despite a lack of interaction effect demonstrated in the models that did not include postnatal controls, it appeared as if there was an interaction when examining a graph of the effects (See Figure 7). When the relationship of maternal cumulative risk during pregnancy and IQ at age 4 was examined in the two allelic conditions, the effect of maternal cumulative risk on child IQ at 4 years was not significant when rs6190 (A/G and A/A) genotypes were present. However, a one unit increase in maternal cumulative risk was associated with a 2.87 decrease in IQ at 4 years in the presence of G/G rs6190 ($p \leq 0.001$) (See Table 33).

IQ at Ages 3 and 4: Cumulative Genetic Risk. When cumulative genetic risk in children was included in models that examined the association of maternal cumulative risk during pregnancy and IQ at age 3, there were no main or interaction effects without and with postnatal controls. However, when cumulative genetic risk was included in models that

examined the association of maternal cumulative risk during pregnancy and IQ at age 4 with postnatal controls, a 1 point increase in maternal cumulative risk during pregnancy was associated with a 1.35 decrease in IQ at age 4 ($p \leq 0.05$) (See Table 34, Model 1). As indicated by the R^2, 36.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for postnatal environment and cumulative genetic risk.

In addition, there was an interaction effect between cumulative genetic risk in children and maternal cumulative risk during pregnancy with postnatal controls ($p \leq 0.05$) (See Table 34, Model 2). As indicated by the R^2, 39.0% of the variation in IQ at age 4 years was predicted by maternal cumulative risk during pregnancy when accounting for postnatal environment, cumulative genetic risk, and interaction terms. When examining a graph of this interaction, it is clear that the addition of reactive alleles that infer risk, whether it's one or two, lead to lower IQ scores in children age 4 years with greater maternal cumulative risk during pregnancy (See Figure 8).

Discussion: Maternal Cumulative Risk and IQ with Genetic Moderation

Using a gene by environment design, this study explored five variants of the glucocorticoid receptor (GR) gene involved in glucocorticoid sensitivity. It is the first to examine the effects of environmental maternal cumulative risk on fetal development with regards to variation in GR gene in children. This study contributes to the growing body of evidence that connects maternal psychosocial and environmental stress during pregnancy with cognitive outcomes in children. Further, it implicates glucocorticoids and their receptors in this causal pathway by demonstrating that the presence of certain glucocorticoid receptor alleles in children moderates the relationship between maternal cumulative risk during pregnancy and child IQ at ages 3 and 4. Specifically, the rs6198 and rs6190 polymorphisms in the GR gene may explain some of the variation in sensitivity to glucocorticoids and, in turn, the consequences of those stress hormones on cognitive development in young children.

In general, rs6198 and rs6190 behaved consistently in their influence on the association between maternal cumulative risk during pregnancy and IQ at both ages 3 and 4. At age 3, results indicated that child IQ decreased to a greater degree in the presence of the rs6198 G allele as compared to when genetic influence was not accounted for. Results also showed that child IQ decreased to a greater degree in the presence of the rs6190 G allele as compared to when genetic influence was not included in models. However, when postnatal controls were included these associations disappeared. It is possible that this trend was due to an underpowered sample or a lack of stability in IQ measurement at age 3. In both rs6198 and rs6190, A alleles were not significant.

At age 4, results appeared to be more robust. Again, child IQ decreased to a greater degree in the presence of rs6198 and rs6190 G alleles, individually. In contrast to age 3, at age

4, the association remained significant when reports of child abuse from birth to age 4 and Caldwell HOME scores at age 4 were accounted for. Also of note, child IQ decreased to a lesser extent in the presence rs6198 A allele as compared to models that did not include genetic influence. Specifically, an increase of 1 unit in cumulative risk during pregnancy was associated with a decrease of 5.08 points in IQ at age 4 years ($p \leq 0.001$) in the presence of the combination of rs6198 genotypes A/G and G/G and a decrease of 1.89 points in IQ at age 4 years ($p \leq 0.01$) in the presence of rs6198 genotype A/A. Thus, rs6198 A and G alleles as well as rs6190 G alleles can be considered reactive. Specifically, rs6198 G and rs6190 G infer risk while rs6198 A serves as a protective factor with respect to the association of maternal cumulative risk during pregnancy and IQ in young children. Finally, when examining cumulative genetic risk, the addition of reactive alleles, whether it's one or two, leads to lower IQ scores in children age 4 years with greater maternal cumulative risk during pregnancy.

As detailed earlier in this paper, work in adult populations has demonstrated an association between functional variants of the GR gene and decreased sensitivity to glucocorticoids while others have shown an association between GR SNPs and increased sensitivity. The findings of this study are consistent with previous literature with respect to the functionality of GR rs6198 and rs6190 G alleles and decreased sensitivity to glucocorticoids. As a result of a lack of receptor sensitivity, it is possible that higher concentrations of circulating glucocorticoids negatively impact fetal brain development. However, GR rs6198 A alleles serve as a protective factor and are associated with a increased sensitivity. In the presence of rs6198 A, it is possible that glucocorticoid receptors have a higher affinity for glucocorticoids, reducing circulating levels of glucocorticoids. Further research in this area is clearly warranted to better understand the biological mechanisms at work. Regardless, the moderation effects of rs6198 and

rs6190 as well as the protective and risky nature of the alleles may contribute to the variability in outcomes seen in previous work.

Limitations

As previously mentioned, there is no consensus on how to measure cumulative risk, in general, as well as women during pregnancy with respect to toxic stress. While there are many common elements, variability exists with regards to singular components of cumulative risk indices. It is possible that relevant risk factors were not included in the maternal cumulative risk index as factor inclusion was limited by the availability of data in the Nurse Family Partnerships Elmira sample. Furthermore, it is possible that specific risk factors have thresholds of impact and risk depending on the coping strategies and abilities of a given family; what could be considered challenging in one family may not be in another.

There may also be limitations in analytic approach with regards to studying cumulative risk versus individual risks. However, as previously mentioned, studies by Rutter (1979), Sameroff and colleagues (1987), and Williams and colleagues (1990) have demonstrated that cumulative disadvantage measures are more predictive than any single risk factor. Theory and prior research tell us that risk factors often are compounded in families and lives producing a snowball effect (Masten, 2011). In the present study, multiple regressions were used to compare the effects of cumulative risk versus singular risk factors on outcome of interest (See Tables 4 and 5). While both models proved significant with respect to IQ at age 4 and total explained variance by both models was similar, it appears that each singular factor was not significant. If any one of these singular elements, unemployment or low income status for example, were not included due to lack of significance, the complete picture of social and emotional stress would not be captured.

Still, the use of cumulative risk indices may not the best means of assessing the combined effects of multiple risks. Recent work in the United Kingdom compared confirmatory factor analysis with formative measurement to a cumulative risk index created from the same risk factors to predict children's cognitive development at 36 and 58 months of age (Hall et al., 2010). Results showed that factor analysis demonstrated greater predictive power of cognitive outcomes in children (Hall et al., 2010). Nonetheless, factor analysis requires a large sample size that is not typical of current research on high-risk populations (Sameroff et al., 2003). The sample size in the current study, in particular, is fairly small and factor analysis may not be prudent.

It is also important to recognize that there is constancy in many of the risk factors included in the maternal cumulative risk index examined in this study. Limitations in data collection did not allow for information on all risk factors to be gathered before and after child birth. As a result, it is not possible to control for the same risks that impacted the mother during pregnancy that may still be present and influential with respect to the child after birth. However, Caldwell HOME scores and reports of child abuse and neglect were included in analyses to account for some of these postnatal risks.

Another limitation of the study is the possibility that the biological mechanisms that give rise to the association of maternal cumulative risk and later child cognitive outcomes are misunderstood. While past research has demonstrated a correlation with cumulative risk and stress hormone levels (Evans et al., 2007), it is possible that the utilized definition of cumulative risk in this study is not a true measure of the antecedents of allostatic load. However, direct biological measures such as cortisol were not available. Still, utilizing a measure of cumulative environmental risk, serving as a precursor to toxic stress and biological impacts, helps to

characterize findings as an opportunity for intervention and risk prevention in the family environment. As a result, early interventions can be better targeted to mitigate risk and support protective factors as opposed to treating biological and developmental outcomes after insult has occurred.

Also, there may be threats to external validity as the community of Elmira, New York is not representative of inner cities or extremely isolated, rural areas. Although the study represents a proportion of women in the United States, there are many for whom these results cannot be applied (e.g. minority populations, such as Hispanic or African American, who register for prenatal care after 30 weeks of gestation). However, there is limited work on low-income, high risk White children who live in rural areas, despite the fact that 53% of poor American children under age 6 live in rural areas and 30% are White (Evans et al., 2007; Wight, Chau, & Aratani, 2010). Although this work contributes the literature with respect to a considerable portion of low-income children, further work examining how these same risk factors may influence other populations such as urban minority samples should be conducted.

While this study includes multiple SNPs from the glucocorticoid receptor gene, a possible limitation is that the project does not examine associated haplotypes. The human genome is an incredibly complex foundation from which multifaceted structures, traits, behaviors, and conditions arise (Grigorenko et al., 2010). It is possible that multiple genetic factors impact the relationship between maternal cumulative risk during pregnancy and IQ in young children as well as other biological influences in this molecular pathway. Analyses of haplotypes appear to provide more information in differentiating groups of interest (i.e. populations with higher vs. lower cumulative risk) and result in a higher power of differentiation. Further, they minimize statistical issues with making multiple comparisons because they require

fewer (Grigorenko et al., 2010). Future steps for this work may include examination of haplotypes in the glucocorticoid receptor gene.

Finally, another limitation of this study is the small nature of the sample size. Due to this challenge, variance was limited. For example, findings with respect to rs6198 may be more robust than rs6190 given available SNP frequencies. Although significant effects were demonstrated, it would be beneficial to replicate these findings in a larger sample that is more diverse in geography, culture, race, and SNPs.

Conclusion and Future Directions

Integration of biological theory and research with social science gives a more complete picture of the ecological context in which families live and strive to flourish. The mechanisms by which environmental impacts on early development are biologically embedded and sustained into childhood will become increasingly important to understand as science is leveraged to design and implement effective interventions in education and health. It is important to recognize that none of the aforementioned processes are deterministic and absolute. For young children who experience toxic stress, interventions that provide specialized services targeted at mitigating environmental risk factors for the family unit as a whole can prevent disruption of brain architecture and promote better developmental outcomes (Center on the Developing Child at Harvard University, 2007). As evidenced by the current study, the prenatal period is an especially important time to mitigate the untoward effects of poverty, as well as other types of chronic stressors, on child development and stimulate positive growth (Liaw & Brooks-Gunn, 1994). Building nurturing family relationships may positively influence a number of domains that make up the complex system of child development. Social support and nurturance can lessen negative effects of toxic stress on the developing fetus both during and after pregnancy (Taylor & Repetti, 1997; Weaver, et al., 2005

Although the protective effects of informal and formal social networks appear to be robust (Cohen, Janicki-Deverts, & Miller, 2007; Collins, Dunkel-Schetter, Lobel, & Scrimshaw, 1993; Gluckman & Hanson, 2005; Rozanski et al., 1999; Sameroff et al., 1987; Taylor & Repetti, 1997), little is known about the quality and quantity of interventions targeted towards mitigating cumulative risk (Shonkoff, Boyce, & McEwen, 2009). Challenge remains in identifying specific influences of risk and developing strategies to mitigate those influences

while promoting protective factors. In general, there is much more known about social and environmental risk and protective factors than genetic ones. More work towards identifying and understanding genetic and environmental influences and the application thereof to policy and programming is incredibly important. As evidenced here, multiple SNPs within a single gene can have very different influences on phenotypes. This is especially relevant in a policy and program context given that the range of phenotypic outcome is impacted by both environment and genetic make-up. Targeted interventions and resources should include an assortment of services to cater to this variability in range. In addition, future research could include more work on factors that promote resiliency by examining measures of cumulative protective factors within the individual and community in which he or she lives.

Further exploration is needed on the cumulative effects of lifelong stress and support with regards to endocrine function, health, and development using larger, more diverse samples of longitudinal data (Flinn & England, 1997; Lupien et al., 2000). This work must include empirically-based measures of allostatic load and/or cumulative risk in adult and child populations to address the lack of consensus in current measures. New research directions could also include examination of the durations of specific stressors within cumulative risk models as well as models of cumulative risk during different developmental periods. It is possible that there could there be periods where certain genotypes are more influential than others with respect to stress.

Emerging research also suggests that early life experiences can cause the attachment and/or detachment of methyl groups to specific regions of genes, reducing gene expression. While phenotypic consequences have yet to be fully defined, epidemiological studies demonstrate that the effects of hyper or hypomethylation can even remain throughout the

lifespan (Harris & Seck, 2011). It is also possible that the effects of this programming are transgenerational if chromosomal and epigenetic changes are stable (Harris & Seckl, 2011). Epigenetic modification presents a new area in which to study the effects of maternal prenatal stress on fetal cognitive development. Further, it provides another outcome for which to design interventions and examine the efficacy of social programs and policy targeted towards prevention of cumulative risk and allostatic load as well as support of protective factors that optimize child health and development.

Through opportunities such as early care and education settings, such as Early Head Start and Head Start, and home visiting programs, the current study supports arguments for greater investment of resources in early intervention opportunities to best target the cumulative effects of a myriad of risk factors that may serve as pathways linking socioeconomic status to health and developmental outcomes (Shonkoff et al., 2009). The importance of maternal health and mental well-being cannot be underscored enough with respect to supporting healthy, happy children. We cannot expect to eliminate the stressors of life nor would that be prudent if we could. The real issue emerges when life events and stress surpass the coping ability of families. Although the science behind it is complicated, competence and resiliency arise from basic adaptive attributes and processes. Only through innovative, multidisciplinary approaches targeted toward families as a unit can we face multidimensional problems and give children the foundations to reach their full potential and contribute to a sustainable society.

. References

Adam, E., Klimes-Dougan, B., & Kudielka, M. (2007). Social regulation of the adrenocortical response. *Human Behavior, Learning, and the Developing Brain: Atypical Development*. Guilford Press.

Anderson, N. & Armstead, C. (1995). Toward understanding the association of socioeconomic status and health: A new challenge for the biopsyhosocial approach. *Psychosomatic Medicine, 57,* 213-225.

Austin, M. & Leader, L. (2000). Maternal stress and obstetric and infant outcomes: Epidemiologic findings and neuroendocrine mechanisms. *Australian & New Zealand Journal of Obstetrics and Gynaecology, 40,* 331-337.

Avishai-Eliner, S., Brunson K., Sandman, C., & Baram, T. (2002). Stressed-out, or in (utero)? *Trends in Neuroscience,* 25, 518–524.

Barker, D. (2007). Obesity and Early Life. *Obesity Reviews, 8,* 45–49.

Barker, D. (2007). The origins of the developmental origins theory (Symposium). *Journal of Internal Medicine, 261,* 412–417.

Barker, D., Eriksson, J., Forson, T., & Osmond, C. (2002). Fetal origins of adult disease: strength of effects and biological basis. *International Journal of Epidemiology, 31,* 1235-1239.

Barnett, W. (1998). Long-term cognitive and academic effects of early childhood education on children in poverty. *Preventive Medicine, 27,* 204-207.

Barrett, J., Fry, B., Maller, J, & Daly, M. (2005). Haploview: Analysis and visualization of LD and haplotype maps. *Bioinformatics Applications Note, 21,* 263-265.

Baser, I., Johnson, T., & Paine, L. (1992). Coupling of fetal movement and fetal heart rate accelerations as an indicator of fetal health. *Obstetrics and Gynecology, 80,* 62-66.

Bauer, A. & Boyce, T. (2004). Prophecies of childhood: How children's social environments and biological propensities affect the health of populations. *International Journal of Behavioral Medicine, 11,* 164-175.

Becker, K. (2003). *History of the Stanford-Binet intelligence scales: Content and psychometrics.* (Stanford-Binet Intelligence Scales, Fifth Edition Assessment Service Bulletin No.1). Itasca, IL: Riverside Publishing.

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? *Molecular Psychiatry, 14,* 746-754.

Bet, P., Penninx, B., Bochdanovits, Z., Uitterlinden, A., Beekman, A., van Schoor, N., Deeg, D., & Hoogendijk, W. (2008). Glucocorticoid receptor gene polymorphisms and childhood adversity are associated with depression: New evidence for a gene-environment interaction. *American Journal of Medical Genetics Part B, 150B,* 660-669.

Bergman, K., Sarkar, P., Glover, V, & O'Connor, T. (2010). Maternal prenatal cortisol and infant cognitive development: Moderation by infant-mother attachment. *Biological Psychiatry, 67,* 1026-1032.

Bourgeois, J., Goldman-Rakic, P., & Rakic, P. (1999). Formation, elimination, and stabilization of synapses in the primate cerebral cortex. In M. Gazzaniga (Ed.), *The New Cognitive Neurosciences* (pp.45-53). Cambridge, MA: MIT Press.

Boyce, W. & Ellis, B. (2005). Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Development and Psychopathology, 17,* 271-301.

Brabham, T., Phelka, A., Zimmer, C., Nash, A., Lopez, J., Vazquez, D. (2000). Effects of prenatal dexamethasone on spatial learning and response to stress is influenced by maternal factors. *American Journal of Physiology. Regulatory, Integrative, Comparative, and Physiology, 279,* R1899-R1909.

Bradley, R. & Caldwell, B. (1979). Home observation for measurement of the environment: A revision of the preschool scale. *American Journal of Mental Deficiency*, 84, 235–244.

Bradley, R. & Caldwell, B. (1980). The relation of home environment, cognitive competence, and IQ among males and females. *Child Development, 51,* 1140-1148.

Bradley, R. & Corwyn, R. (2002). Socioeconomic status and child development. *Annual Review of Psychology, 53,* 371-399.

Brooks-Gunn, J. (1991). Stress and support during pregnancy: What do they tell us about low birth weight? In H. Berendes, S. Kessel, & S. Yaffe (Eds.), *Advances in Low Birth weight: An International Symposium* (pp. 39-57). Washington D.C.: National Center for Education in Maternal and Child Health.

Brooks-Gunn, J. & Duncan, G. (1997). The effects of poverty on children. *The Future of Children: Children and Poverty, 7,* 55-77.

Brooks-Gunn, J., Klebanov, P., Liaw, F., & Spiker, D. (1993). Enhancing the development of low-birth weight, premature infants: Changes in behavior and cognition over the first three years. *Child Development, 64*, 736-753.

Brouwers, E., van Baar, A., & Pop, V. (2001). Maternal anxiety during pregnancy and subsequent infant development. *Infant Behavior & Development, 24*, 95-106.

Caldwell, B. & Bradley, R. (1979). *Home observation for measurement of the home environment*. Little Rock, AR: University of Arkansas.

Catalini, A., Casolini, P., Cigliana, G., Scaccianoce, S., Consoli, C., Cinque, C., et al. (2002). Maternal corticosterone influences behavior, stress response, and corticosteroid receptors in the female rat. *Pharmacology, Biochemistry, and Behavior, 73,* 105-114.

Center on the Developing Child at Harvard University. (2007). *A Science-Based Framework for Early Childhood Policy: Using Evidence to Improve Outcomes in Learning, Behavior, and Health for Vulnerable Children*. Retrieved from http://www.developingchild.harvard.edu.

Challis, J., Matthews, S, Gibb, W., & Lye S. (2000). Endocrine and paracrine regulation of birth at term and preterm. *Endocrine Review, 21*, 514–550.

Child Trends. (2010). Census reports more children living in poverty: Implications for well-being. *Research Update*. Retrieved from http://archive.constantcontact.com/fs008/1101701160827/archive/1103693115054.html.

Coe, C., Kramer, M., Czeh, B., Gould, E., Reeves, A., Kirschbaum, C., et al. (2003). Prenatal stress diminishes neurogenesis in the dentate gyrus of juvenile rhesus monkeys. *Biological Psychiatry, 54*, 1025-1034.

Cohen, S., Janicki-Deverts, D., & Miller, G. (2007). Psychological stress and disease. *Journal of the American Medical Association, 298*(14), 1685-1687.

Cohen, S., Kessler, R., & Gordon, U. (1995). Strategies for measuring stress in studies of psychiatric and physical disorder. In S., Cohen, R., Kessler, & U, Gordon (Eds.), *Measuring Stress: A Guide for Health and Social Scientists* (pp.3-26). New York, NY: Oxford University Press.

Collins, N., Dunkel-Schetter, C., Lobel, M., & Scrimshaw, S. (1993). Social support in pregnancy: psychosocial correlates of birth outcomes and postpartum depression. *Journal on Perspectives of Social Psychology, 65*, 1243-1258.

Costantini, D., Marasco, V., & Moller, A. (2011). A meta-analysis of glucocorticoids as modulators of oxidative stress in vertebrates. *Journal of Comparative Physiology B: Biochemical, Systemic, and Environmental Physiology, 181*, 447-456.

Davis, E. & Sandman, C. (2010). The timing of prenatal exposure to maternal cortisol and psychosocial stress is associated with human infant cognitive development. *Child Development, 81*(1), 131-148.

Davis, E., Snidman, N., Wadhwa, P., Glynn, L., Dunkel-Schetter, C., & Sandman, C. (2004). Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy, 6*, 319-331.

DeNavas-Walt, C., Proctor, B., & Smith, J. (2011). U.S. Census Bureau, Current Population Reports, *Income, Poverty, and Health Insurance Coverage in the United States: 2010*, U.S. Government Printing Office, Washington, DC.

De Kloet, E., Sibung, R., Helmerhorst, F., & Schmidt, M. (2005). Stress, genes and the mechanisms of programming the brain for later life. *Neuroscience and Biobehavioral Reviews, 29*, 271-281.

DeRijk, R. & de Kloet, E. (2008). Corticosteroid receptor polymorphisms: Determinants of vulnerability and resilience. *European Journal of Pharmacology, 583*, 303-311.

De Rijk, R. (2009). Single nucleotide polymorphisms related to HPA axis reactivity. *Neuroimmunomodulation, 16*, 340–352.

De Rijk, R., Katraki, E.,& DeKoet, E. (2010). Corticosteroid hormones in stress and anxiety—Role of receptor variants and environmental inputs. In H. Soreq, A. Friedman, & D. Kaufer (Eds.), *Stress—From Molecules to Behavior: A Comprehensive Analysis of the Neurobiology of Stress Responses* (pp. 119-142). Germany: Wiley-Blackwell.

De Rijk, R., Wust, S., Meijer, O., Zannaro, M., Federenko, I., Helhammer, D., Giachetti, G., Vreugdenhil, E., Zitman, F., de Kloet, E. (2006). A common polymorphism in the mineralocorticoid receptor modulates stress responsiveness. *Journal of Clinical Endocrinology and Metabolism*, 91, 5083-5089.

Desai, M. & Hales, C. (1997). Role of fetal and infant growth in programming metabolism in later life. *Biological Review, 72*, 329-348.

DiPietro, J., Novak, M., Costigan, K., Atella, L., & Reusing, S. (2006). Maternal psychological distress during pregnancy in relation to child development at age two. *Child Development, 77*, 573-587.

DiPietro, J., Kivlighan, K., Costigan, K., Rubin, S., Shiffler, D., Henderson, J., & Pillion, J. (2010). Prenatal antecedents of newborn neurological maturation. *Child Development*, 81(1), 115-130.

Dobbing, J. (1981). The later development of the brain and its vulnerability. In J. Davis & J. Dobbing (Eds.), *Scientific Foundations of Paediatrics* (pp.744-759). London: Heinemann Medical Books.

Dubowitz, L., Dubowitz, V., & Goldberg, C. (1970). Clinical assessment of gestational age in the newborn infant. *Journal of Pediatrics,* 77.

Eriksen, M., Bakken, M., Espmark, A., Braastad, B., & Salte, R. (2006). Prespawning stress in farmed Atlantic salmon *Salmo salar*: Maternal cortisol exposure and hyperthermia during embryonic development affect offspring survival, growth, and incidence of malformations. *Journal of Fish Biology, 69*, 114-129.

Evans, G. & Kim, P. (2010). Multiple risk exposure as a potential explanatory mechanism for the socioeconomic-health gradient. *Annuls of the New York Academy of Sciences, 1186,* 174-189.

Evans, G., Kim, P., Ting, A., Tesher, H., & Shannis, D. (2007). Cumulative risk, maternal responsiveness, and allostatic load among young adolescents. *Developmental Psychology, 43*(2), 341-351.

Finken, M., Meulenbelt, I., Dekker, F., Frölich, M., Romijn, J., Slagboom, P., & Wit, J. on behalf of the Dutch POPS-19 Collaborative Study Group. (2007). The 23K variant of the R23K polymorphism in the glucocorticoid receptor gene protects against postnatal growth failure and insulin resistance after preterm birth. *Journal of Clinical Endocrinology Metabolism, 92*, 4777–4782.

Fan, J., Oliphant, A., Shen, R., Kermani, B., Garcia, F., Gunderson,K., Hansen,M., Steemers,F., Butler, S., Deloukas P., Galver,L., Hunt,S., McBride,C., Bibikova, M., Rubano, T., Chen,J., Wickham, E., Doucet, D., Chang, W., Campbell, D., Zhang, B., Kruglyak,S., Bentley, D., Haas, J., Rigault, P., Zhou,L., Stuelpnagel, J., & Chee, M. (2003). Highly parallel SNP genotyping. *Cold Spring Harbor Symposia on Quantitative Biology,* LXVIII.

Flinn, M. & England, B. (1997). Social economics of childhood glucocorticoid stress responses and health. *American Journal of Physical Anthropology, 102,* 33–53.

Fowden, A., Giussani, D., & Forhead, A. (2006). Intrauterine programming of physiological systems: Causes and consequences. *Physiology, 21*(1), 29-37.

Fox, S., Levitt, P., & Nelson, C. (2010). How the timing and quality of early experiences influence the development of brain architecture. *Child Development, 81*(1), 28-40.

Fox, N. & Rutter, M. (2010). Introduction to the special section on the effects of early experience on development. *Child Development, 81*(1), 23-27.

Glover, V., O'Connor, T., & O'Donnell. (2010). Prenatal stress and the programming of the HPA axis. *Neuroscience and Biobehavioral Reviews, 35*, 17-22.

Gluckman, P. & Hanson, M. (2005). *The Fetal Matrix: Evolution, Development, and Disease*. United Kingdom: Cambridge University Press.

Grigorenko,E., DeYoung,C., Eastman, M., Getchell, M., Haeffel, G., af Klinteberg, B., Koposov, R., Oreland, L., Pakstis, A., Ponomarev, O., Ruchkin, V., Singh, J., and Yrigollen, C. (2010). Aggressive behavior, related conduct problems, and variation in genes affecting Dopamine turnover. *Aggressive Behavior, 36,* 158-176.

Grigorenko, E., DeYoung, C., Getchell, M., Haeffel, G., af Klinteberg, B., Koposov, R., Oreland, L., Pakstis, A., Ruchkin, V. & Yrigollen, C. (2007). Exploring interactive effects of genes and environments in etiology of individual differences in reading comprehension. *Developmental Psycholpathology, 19*, 1089-1103.

Grossman, A., Churchill, J., McKenney, B., Kodish, I., Otte, S., & Greenough, W. (2003). Experience effects on brain development: Possible contributions to psychopathology. *Journal of Child Psychology and Psychiatry, 44*, 33-63.

Gunnar, M. & Quevedo, K. (2007). The neurobiology of stress and development. *Annual Review of Psychology, 58*, 145-173.

Gunnar, M., Fisher, P., and The Early Experience, Stress, and Prevention Network. (2006). Bringing basic research on early experience and stress neurobiology to bear on preventative interventions for neglected and maltreated children. *Development and Psychopathology, 18*, 651-677.

Gutteling, B., de Weerth, C., & Buitelaar, J. (2005). Prenatal stress and children's cortisol reaction to the first day of school. *Psychoneuroendocrinology, 30*, 541–549.

Gutteling, B., de Weerth, C., Willemsen-Swinkels, S., Huizink, A., Mulder, E., Visser, G., et al. (2005). The effects of prenatal stress on temperament and problem behavior of 27-month-old toddlers. *European Child and Adolescent Psychiatry, 14*, 41-51.

Gutteling, B., de Weerth, C., Zandbelt, N., Mulder, E., Visserand, G., & Buitelaar, J. (2006). Does maternal prenatal stress adversely affect the child's learning and memory at age 6? *Journal of Abnormal Psychology, 34*, 789-798.

Hack, M., Breslau, N., Weissman, B., Aram, D., Klein, N., & Borawski, E. (1991). Effect of very low birth weight and subnormal head size on cognitive abilities at school age. *The New England Journal of Medicine, 325*, 231-237.

Hack, M., Flannery, D., Schluchter, M., Cartar, L., Borawski, E., & Klein, N. (2002). Outcomes in young adulthood for very-low-birth-weight infants. *The New England Journal of Medicine, 346*, 149-157.

Hack, M., Taylor, G., Klein, N., Eiben, R., Schatschneider, C., & Mercuri-Minich, N. (1994). School-age outcomes in children with birth weights under 750 g. *The New England Journal of Medicine, 331*, 753-759.

Hackman, D., Farah, M., & Meaney, M. (2010). Socioeconomic status and the brain: mechanistic insights from human and animal research. *Nature Reviews, 11*, 651-659.

Hall, J., Sammons, P., Sylva, K., Melhuish, E., Taggart, B., Siraj-Blatchford, I., & Smees, R. (2010). Measuring the combined risk to young children's cognitive development: An

alternative to cumulative indices. *British Journal of Developmental Psychology, 28*, 219-238.

Hammock, E. & Levitt, P. (2006). The discipline of neurobiological development: The emerging interface that builds processes and skills. *Human Development, 49*, 294-309.

Harburg, E., Erfurt, J., Havenstein, L., Chape, S., Schull, W., & Schork, M. (1993). Sociological stress, suppressed hostility, skin color, and black-white make blood pressure: Detroit. *Psychosomatic Medicine, 35*, 176-196.

Harris, A. & Seckl, J. (2011). Glucocorticoids, prenatal stress and the programming of disease. *Hormones and Behavior, 59*, 279-289.

Hauser , J., Dettling-Artho, A., Pilloud, S., Maier, C., Feldon, J., & Pryce, C. (2007). Effects of prenatal dexamethasone treatment on postnatal physical, endocrine, and social development in the common marmoset monkey. *Endocrinology, 148*, 1813-1822.

Hedges, D. & Woon, F. (2011). Early-life stress and cognitive outcome. *Psychopharmacology, 214*, 121-130.

Henry, C., Kabbaj, M., Simon, H., Le Moal, M., & Maccari,S. (1994). Prenatal stress increases the hypothalmo-pituitary-adrenal axis response in young and adult rats. *Journal of Neuroendocrinology, 6*, 341-345.

Hosseini-Sharifabad, M. & Hadinedoushan, H. (2007). Prenatal stress induces learning deficits and is associated with a decrease in granules and CA3 cell dendritic tree size in rat hippocampus. *Anatomical Science International, 82*, 211-217.

Huizink, A., Robles de Medina, P, Mulder, E., Visser, G., & Buitelaar, J. (2003). Stress during pregnancy is associated with developmental outcomes in infancy. *Journal of Child Psychology and Psychiatry, 44*, 810-818.

Ingles, S. (2004). [Ed. Thomas, D.] *Statistical Methods in Genetic Epidemiology*. New York: Oxford Press.

Johnson, T., Besinger, R., Thomas, R., Strobino, D., & Niebyl, J. (1992). Quantitative and qualitative relationships between fetal heart rate accelerations and fetal movement. *Journal of Maternal-Fetal & Neonatal Medicine, 1,* 251—253.

Kapoor, A., Dunn, E., Kostaki, A., Andrews, M., & Matthews, S. (2006). Fetal programming of hypothalamo-pituitary-adrenal function: Prenatal stress and glucocortocoids. *Journal of Physiology, 572*, 31-44.

King, B., Nicholson, R., & Smith, R. (2001). Placental corticotrophin-releasing hormone, local effects of fetomaternal endocrinology. *Stress, 4*, 219-233.

Kivimaki, M., Virtanen, M., Elovainio, M, Kouvonen, A., Vaananen, A., & Vahtera, J. (2006). Work stress in the etiology of coronary heart disease—a meta-analysis. *Scandinavian Journal of Work and Environmental Health,* 32, 431-442.

Klebanov, P. & Brooks-Gunn, J. (2006). Cumulative, human capital, and psychological risk in the context of early intervention: Links with IQ at ages 3, 5, and 8. *Annals of New York Academy of Sciences, 1094*, 63-82.

Kudielka, B. & Kirschbaum, C. (2005). Sex differences in HPA axis responses to stress: A review. *Biological Psychology,* 69, 113-132.

Kuningas, M., Mooijaart, S., Slagboom, P., Westendorp, R., & Heemst, D. (2006). Genetic variants in the glucocorticoid receptor gene (NR3C1) and cardiovascular disease risk: The Leiden 85-plus study. *Biogerontology,* 7, 231–238.

Laplante, D., Barr, R., Brunet, A., DuFort, G., Meaney, M., Saucier, J., et al. (2004). Stress during pregnancy affects general intellectual and language functioning in human toddlers. *Pediatric Research, 56,* 185-190.

Levitt, P. (2003). Structural and functional maturation of the developing primate brain. *Journal of Pediatrics, 143*, S35-S45.

Liaw, F. & Brooks-Gunn, J. (1994). Cumulative familial risks and low-birth weight children's cognitive and behavioral development. *Journal of Clinical Child Psychology, 23*, 360-372.

Liggins, G. (2000). The role of the hypothalamic-pituitary-adrenal axis in preparing the fetus for birth. *American Journal of Obstetrics and Gynecology, 182*, 475–477.

Liu, D., Diorio, J., Day, J., Francis, D., & Meaney, M. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience, 3*, 799-806.

Lou, X., Chen, G., Yan, L., & Li, M. (2007). *GMDR User Reference Manual: GMDR Software Beta Version 0.7*. Charlottsville, VA: University of Virginia Health System.

Lupien, S. King, S., Meaney, M., & McEwen, B. (2000). Child's stress hormone levels correlate with mother's socioeconomic status and depressive state. *Biological Psychiatry, 48*, 976-980.

MacArthur Research Network on Socioeconomic Status and Health. (2005). *SES and Health across the Lifespan*. Retrieved from http://www.macses.ucsf.edu.

Maccari, S., Piazza, P., Kabbaj, M., Barbazanges, A., Simon, H., & Le Moal, M. (1995). Adoption reverses the long-term impairment in glucocorticoid feedback induced by prenatal stress. *Journal of Neuroscience, 15*, 110-116.

Manenschijn, L., van den Akker, E., Lamberts, S., & van Rossum, E. (2009). Clinical Features Associated with Glucocorticoid Receptor Polymorphisms: An Overview, *Annals of the New York Academy of Sciences, 1179,* 179-198.

Masten, A. (2011, November). *Risk and Resilience in Development.* Presented at Workshop on the Scientific Study of Military Children, Washington, DC.

McCormick, M., Brooks-Gunn, J., Workman-Daniels, K., Turner, J., & Peckham, G. (1992). The health and developmental status of very-low-birth weight children at school age. *The Journal of the American Medical Association, 267,* 2204-2208.

McEwen, B. (1998). Protective and damaging effects of stress mediators. *New England Journal of Medicine, 338,* 171-179.

McEwen, B. (2000). Allostasis and allostatic load: Implications for neuropsychopharmacology. *Neuropsyhcopharmacology, 22,* 108-124.

McEwen, B. (2007). Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiological Reviews, 87,* 873-904.

McEwen, B. & Seeman, T. (1999). Protective and damaging effects of mediators of stress. *Annals of the New York Academy of Sciences, 896,* 30–47.

McEwen, B. & Stellar, E. (1993). Stress and the individual: Mechanisms leading to disease. *Archives of Internal Medicine, 153,* 2093-2101.

Meaney, M. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81,* 41-79.

Meaney, M., Szyf, M., & Seckl, J. (2007). Epigenetic mechanisms of perinatal programming of hypothalamic-pituitary-adrenal function and health. *Trends in Molecular Medicine, 13,* 269-277.

Melamed, B. (1995). Special section: The interface of mental and physical health. *Health Psychology, 14,* 371-426.

Meylan, S. & Clobert, J. (2005). Is corticosterone-mediated phenotype development adaptive? – maternal corticosterone treatment enhances survival in male lizards. *Hormones and Behavior, 48,* 44-52.

Mohler, E., Parzer, P, Brunner, R., Wiebel, A., & Resch, F. (2006). Emotional stress in infancy predicts human infant reactivity. *Early Human Development, 82,* 731-737.

Mueller, B. & Bale, T. (2008). Sex-specific programming of offspring emotionality after stress early in pregnancy. *Journal of Neuroscience, 28,* 9055-9065.

Murani, E., Ponsuksili, S., D'Eath, R., Turner, S., Kurt, E., Evans, G., Thölking, L., Klont, R., Foury, A., Mormède, P., &, Wimmers, K. (2010). Association of HPA axis-related genetic variation with stress reactivity and aggressive behavior in pig. *BMC Genetics, 11*, 1-11.

Narberhaus, A., Segarra, D., Caldu, X., Gimenez, M., Junque, C., Pueyo, R., & Botet, F. (2007). Gestational age at preterm birth in relation to corpus callosum and general cognitive outcome in adolescents. *Journal of Child Neurology, 22*, 761-765.

National Center for Biotechnology Information (NCBI). (2010). Retrieved from http://www.ncbi.nlm.nih.gov/.

National Scientific Council on the Developing Child. (2005). Excessive Stress Disrupts the Architecture of the Developing Brain: Working Paper #3. Retrieved from http://www.developingchild.net.

Oitzl, M., Champagne, D., van der Veen, R., & de Kloet, E. (2010). Brain development under stress: Hypotheses of glucocorticoid actions revisited. *Neuroscience and Biobehavioral Reviews, 34*, 853-866.

Olds, D. (2002). Prenatal and infancy home visiting by nurses: From randomized trials to community replication. *Prevention Science, 3*, 153-172.

Olds, D., Comprehensive Developmental Services, Inc., Henderson, C., Birmingham, M., Chamberlain, R., & Tatelbaum, R. (1983). *Final report: Prenatal/Early Infancy Project* (MCH/CC-83). Springfield, Virginia: National Technical Information Services, U.S. Department of Commerce.

Olds, D., Henderson, C., Chamberlin, R., & Tatelbaum, R. (1986). Preventing child abuse and neglect: A randomized trial of nurse home visitation. *Pediatrics, 78*, 65-78..

Olds, D., Henderson, C., & Tatelbaum, R. (1994). Intellectual impairment in children of women who smoke cigarettes during pregnancy. *Pediatrics, 93*, 221-227.

O'Connor, T., Ben-Shlomo, Y., Heron, J., Golding, J., Adams, D., & Glover V. (2005). Prenatal anxiety predicts individual differences in cortisol in pre-adolescent children. *Biological Psychiatry, 58*, 211–217.

Plomin, R., Defries, J., McClearn, G, & McGuffin, P. (2008). *Behavioral Genetics*, 5th Edition. New York: Worth Publishers.

Power, M., Bowman, M., Smith, R., Ziegler, T., Layne, D., Schulkin, J., et al. (2006). Pattern of maternal serum corticotrophin-releasing hormone concentration during pregnancy in the most common marmoset (*Callithrix jacchus*). *American Journal of Primatology, 68*, 181-188.

Power, M. & Tardiff, S. (2005). Maternal nutrition and metabolic control of pregnancy. In M. Power & J. Schulkin (Eds.), *Birth, Distress and Disease* (pp.88-113). Cambridge, United Kingdom: Cambridge University Press.

Rautanen, A., Eriksson, J., Kere, J., Andersson, S., Osmond, C., Tienari, P., Sairanen, H., Barker, D., Phillips, D., Forsen, T., & Kajantie, E. (2006). Associations of body size at birth with late-life cortisol concentrations and glucose tolerance are modified by haplotypes of the glucocorticoid receptor gene. *The Journal of Clinical Endocrinology & Metabolism, 91*, 4544–4551.

Repetti, R., Taylor, S., & Seeman, T. (2002). Risky families: Family social environments and the mental and physical health of offspring. *Psychological Bulletin, 128*, 330-366.

Rosmond, R. (2002). The glucocorticoid receptor gene and its association to metabolic syndrome. *Obesity Research, 10*, 1078–1086.

Rotter, J. (1966). General expectancies for internal versus external locus of reinforcement. *Psychology Monographs: General and Applied, 80*.

Rozanski, A., Blumenthal, J., & Kaplan, J. (1999). Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. *Circulation*, 99(16), 2192-2217.

Russcher, H., Smit, P., van den Akker, E., van Rossum, E., Brinkman, A., de Jong, F., Lamberts, S., & Koper, J. (2005). Two polymorphisms in glucocorticoid receptor gene directly affect glucocorticoid-regulated gene expression. *Journal of Clinical Endocrinology and Metabolism, 90*, 5804-5810.

Rutter, M. (1979). Protective factors in children's responses to stress and disadvantage. In M. Kent & J. Rolf (Eds.), *Primary Prevention of Psychopathology. III. Social Competence in Children* (pp.49-74). Hanover, NH: University Press of New England.

Rutter, M. (2006). *Genes and behavior: Nature-nurture interplay explained*, 144-155. Blackwell Publishing: Malden, MA.

Sameroff, A., Gutman, L., & Peck, S. (2003). Adaptation among youth facing multiple risks. In S. Luthar (Ed.), *Resilience and Vulnerability: Adaptation in the Context of Childhood Adversities* (pp. 364-391). Cambridge: Cambridge University Press.

Sameroff, A., Seifer, R., Barocas, R., Zax, M., & Greenspan, S. (1987). Intelligence Quotient scores of 4-year-old children: Social-environmental risk factors. *Pediatrics, 79*, 343-350.

Sandman, C., Davis, E., Buss,C., & Glynn, L. (2011). Exposure to prenatal psychobiological stress exerts programming influences on the mother and her fetus. *Neuroendocrinology* eprint, http://content.karger.com/produktedb/produkte.asp?DOI=000327017&typ=pdf

Sapolsky, R., Romero, L., & Munck, A. (2000). How do glucocorticoids influence stress response? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews, 21*, 55-89.

Sattler, J. (1992). *Assessment of children's intelligence and special abilities*. Boston: Allyn & Bacon.

Schneider, M. (1992). Delayed object permanence development in prenatally stressed rhesus monkey infants (*Macaca mulatta*). *Occupational Therapy Journal of Research, 12*, 96-110.

Schneider, M., Moore, C., Kraemer, G., Roberts, A., & DeJesus, O. (2002). The impact of prenatal stress, fetal alcohol exposure, or both on development: Perspectives from a primate model. *Psychoneuroendocrinology, 27*, 285-298.

Schwartz, J. (1994). Low-level lead exposure and children's IQ: A meta-analysis and search for a threshold. *Environmental Research, 65*, 42-55.

Seckl, J. (2008). Glucocorticoids, developmental 'programming', and the risk of affective dysfunction. *Progress in Brain Research, 167*, 17-34.

Seckl, J., Cleasby, M., & Nyirenda M. (2000). Glucocorticoids, 11β-hydroxysteroid dehydrogenase, and fetal programming. *Kidney International, 57*, 1412–1417.

Seckl, J., Drake, A., & Holmes, M. (2005). Prenatal glucocorticoids and the programming of adult disease. In M. Power & J. Schulkin (Eds.), *Birth, Distress and Disease* (pp.88-113). Cambridge, United Kingdom: Cambridge University Press.

Seckl, J. & Holmes, M. (2007). Mechanisms of disease: Glucocorticoids, their placental metabolism and fetal "programming" of adult pathophysiology. *Nature Clinical Practice Endocrinology & Metabolism, 3*, 479-488.

Seeman, T., Berkman, L, Blazer, D., & Rowe, J. (1994). Social ties and support and neuroendocrine function: MacArthur Studies of Successful Aging. *Annuls of Behavioral Medicine, 16*, 95-106.

Selye, H. (1956). *The Stress of Life*. New York: McGraw-Hill.

Shonkoff, J. (2006). A promising opportunity for developmental and behavioral pediatrics at the interface of neuroscience, psychology, and social policy: Remarks on receiving the 2005 C. Anderson Aldrich Award. *Pediatrics, 118*, 2187-2191.

Shonkoff, J., Boyce, W., & McEwen, B. (2009). Neuroscience, molecular biology, and the childhood roots of health disparities: Building a new framework for health promotion and disease prevention. *Journal of the American Medical Association, 301*, 2252-2259.

Simmons, R. (2008). Perinatal programming of obesity. *Seminars in Perinatology, 32*, 371-374.

Spijker, A. & van Rossum, E. (2009). Glucocorticoid receptor polymorphisms in major depression: Focus on glucocorticoid sensitivity and neurocognitive functioning. *Annals of the New York Academy of Sciences, 1179,* 199-215.

Stanwood, G. & Levitt, P. (2008). The effects of monoamines on the developing nervous system. In C. Nelson & M. Luciana (Eds.), *Handbook of Developmental and Cognitive Neuroscience* (2nd ed., pp.83-94). Cambridge, MA: MIT Press.

Stephens, M., Smith, N., & Donnelly, P. (2001). A new statistical method for haplotype reconstruction from population data. *American Journal of Human Genetics, 68,* 978-989.

Sternberg, R., Grigorenko, E., & Bundy, D. (2001). The predictive value of IQ. *Merrill-Palmer Quarterly, 47,* 1-41.

Taylor, S. & Repetti, R. (1997). Health Psychology: What is an Unhealthy Environment and How Does It Get Under the Skin? *Annual Reviews of Psychology, 48,* 411-447.

Totsika, V. & Sylva, K. (2004). The Home Observation for Measurement of the Environment revisited. *Child and Adolescent Mental Health, 9,* 25–35.

University of California, Los Angeles: Academic Technology Services, Statistical Consulting Group. (2010). *Stata Library: Multiple Imputation Using ICE*. Retrieved from http://www.ats.ucla.edu/stat/stata/library/ice.htm.

United States Department of Health and Human Services. Office of Disease Prevention and Health Promotion. (2011). Healthy People 2020. Washington, DC.

Uno, H., Eisele, S., Sakai, A., Shelton, S, Baker, E., De-Jesus, O., et al. (1994). Neurotoxicity of glucocorticoids in the human brain. *Hormone and Behavior, 28,* 336-348.

Uno, H., Tarara, R., Else, G., Suleman, M., & Sapolsky, R. (1989). Hippocampal damage associated with prenatal glucorticoid exposure. *Journal of Neuroscience, 9,* 1705-1711.

Vallee, M., MacCari, S., Dellu, F., Simon, H., Le Moal,M., & Mayo, W. (1999). Long-term effects of prenatal stress and postnatal handling on age-related glucocorticoid secretion and cognitive performance: A longitudinal study in the rat. *European Journal of Neuroscience, 11,* 2906-2916.

Van den Bergh, B., Mulder, E., Mennes, M., & Glover, V. (2005). Antenatal maternal anxiety and stress and the neurobehavioral development of the fetus and child: Links and possible mechanisms. A review. *Neuroscience and Biobehavioral Review, 29,* 237-258.

Van Rossum, E., Roks, P., de Jong, F., Brinkmann, A., Pols, H., Koper, J., & Lamberts, S. (2004). Characterization of a promoter polymorphism in the glucocorticoid receptor gene and its relationship to three other polymorphisms. *Clinical Endocrinology, 61,* 573-581.

Van Rossum, E., Koper, J., Huizenga, N., Uitterlinden, A., Janssen, J., Brinkmann, A., Grobbee, D., de Jongh, F., van Duyn, C., Pols, H., & Lamberts, S. (2002). A polymorphism in the glucocorticoid receptor gene, which decreases sensitivity to glucocorticoids in vivo, is associated with low insulin and cholesterol levels. *Diabetes, 51,* 3128–3134.

Van Rossum, E. & van den Akker, E. (2011). Glucocorticoid Resistance. In L. Ghizzoni, M. Cappa, G. Chrousos, S. Loche, & M. Maghnie M (Eds.), *Pediatric Adrenal Diseases* (pp 127–136). Switzerland: S.Karger AG.

Seckl, J., Drake, A., & Holmes, M. (2005). Prenatal glucocorticoids and the programming of adult disease. In M. Power & J. Schulkin (Eds.), *Birth, Distress and Disease* (pp.88-113). Cambridge, United Kingdom: Cambridge University Press.

Wada, H., Salvante, K., Stables, C., Wagner, E., Williams, T., Breuner, C. (2008). Adrenocortical responses in zebra finches (*Taeniopygia guttata*): Individual variation, repeatability, and relationship to phenotypic quality. *Hormonal Behavior, 53*, 472-480.

Wadhwa, P., Culhane, J., Rauh , V., & Barve, S. (2001). Stress and preterm birth: neuroendocrine, immune/inflammatory, and vascular mechanisms. *Journal of Maternal and Child Health, 5*, 119–125.

Weaver, I., Champagne, F., Brown, S., et al. (2005). Reversal of maternal programming of stress responses in adult offspring through methyl supplementation: altering epigenetic marking later in life. *Journal of Neuroscience, 25*, 11045–11054.

Weinstock, M., Matlina, E., Maor, G., Rosen, H., & McEwen, B. (1992). Prenatal stress selectively alters the reactivity of the hypothalamic-pituitary adrenal system in the female rat. *Brain Research, 595*, 195–200.

Welberg, L. & Seckl, J. (2001). Prenatal stress, glucocorticoids, and the programming of the brain. *Journal of Neuroendocrinology, 13*, 113-128.

Welberg, L., Thrivikraman, K., & Plotsky P. (2005). Chronic maternal stress inhibits the capacity to up-regulate placental 11beta-hydroxysteroid dehydrogenase type 2 activity. *Journal of Endocrinology, 186*, R7–R12.

Wight, V., Chau, M., & Aratani, Y. (2010). *Who Are America's Poor Children? The Official Story.* New York, NY: National Center for Children in Poverty, Columbia University, Mailman School of Public Health.

Willerman, L. (1972). Biosocial influences on human development. *American Journal of Orthopsychiatry, 42*.

Williams, S., Anderson, J., McGee, R., & Silva, P. (1990). Risk factors for behavioral and emotional disorder in preadolescent children. *Journal of the American Academy of Child Adolescent Psychiatry, 29*, 413-419.

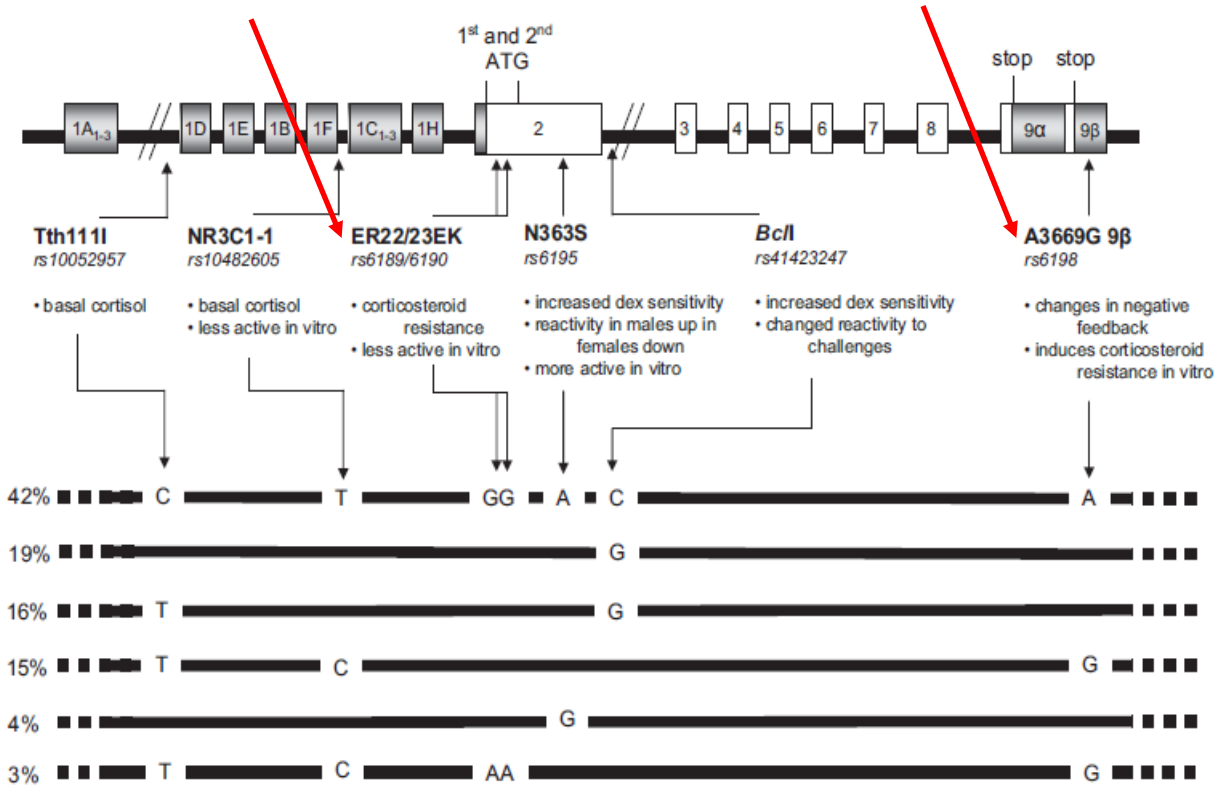
Wulczyn, F. Barth , R., Yuan, Y., Jones Harden, B., & Landsverk, J. (2005). Altering the Early Life Course of Children in Child Welfare. *Beyond Common Sense: Child Welfare, Child Well-Being, and the Evidence for Policy Reform*. New Brunswick: Aldine Transaction.

Yang, J., Han, H., Cao, J., Li, L., & Xu, L. (2006). Prenatal stress modifies hippocampal synaptic plasticity and spatial learning in young rat offspring. *Hippocampus, 16*, 431-436.

Ziegler, A. & Konig, I. (2010). *A Statistical Approach to Genetic Epidemiology*. Germany: Wiley-Blackwell

Appendix

Figure 1. Glucocorticoid Receptor Gene



(DeRijk, 2009)

Table 1.
Characteristics of mothers in full sample and sample in which DNA was collected

	Full Sample			DNA Sample		
	N	Mean(SD)/%	Range	N	Mean(SD)/%	Range
Nurse Family Partnership Program[1]	398			241		
Treatment		54.3%			50.2%	
Control		45.7%			49.8%	
Maternal education level[1]	398	11.2 (1.6)	6.0-17.0	241	11.2 (1.5)	6.0-16.0
Did not graduate from high school		45.0%			45.2%	
Graduated from high school		55.0%			54.8&	
Maternal employment[1]	330			235		
Employed		32.7%			34.9%	
Unemployed		67.3%			65.1%	
Marital status[1]	398			241		
Married		38.4%			38.2%	
Unmarried		61.6%			61.8%	
Maternal age[1]	398	19.4 (3.2)	13.0-34.0	241	19.1 (2.9)	13.0-31.0
19 years old and younger		60.3%			63.1%	
20 years old and older		39.7%			36.9%	
Maternal race[1]	398			241		
White		88.7%			88.8%	
Non-White		11.3%			11.2%	
Annual household income in 1977 dollars[1]	313	7368.3 (5996.7)	0.0-31044.0	193	7061.6 (5767.2)	0.0-31044.0
Below 1977 federal poverty level		34.8%			36.3%	
Above 1977 federal poverty level		65.2%			63.7%	
Number of people in support network[1]	396	1.8 (1.5)	0.0-10.0	239	1.7 (1.4)	0.0-8.0
No support		12.4%			12.6%	
Some support		87.6%			87.4%	
Number of members in household[1]	396	1.2 (1.0)	0.0-7.0	239	1.3 (0.9)	0.0-4.0
Mother lives alone		18.7%			16.3%	
Mother lives with one or more people		81.3%			83.7%	
Maternal cigarettes per day[1]	398	6.8 (9.2)	0.0-55.0	241	6.4 (8.5)	0.0-40.0
Maternal Nutrient Adequacy Reporting Index (NARS) [2]	398	73.2 (18.6)	14.0-100.0	241	71.8 (18.8)	14.0-100.0
Criminal engagement[2]	398			241		
Yes		26.6%			17.8%	
No		73.4%			82.2%	
Homeless[2]	306			205		
Yes		4.6%			2.0%	
No		95.4%			98.0%	
Relationship problems[2]	398			241		
Yes		46.5%			41.1%	
No		53.5%			58.9%	
General life anxiety[2]	358	19.6 (5.7)	2.0-37.0	228	19.4 (5.7)	2.0-37.0
Maternal cumulative risk[3]	220	4.2 (2.1)	0.0-9.0	157	4.3 (2.0)	0.0-9.0
0 risks	3	1.4%		2	1.2%	
1 risk	16	7.3%		10	6.4%	
2 risks	32	14.6%		22	14.0%	
3 risks	41	18.6%		23	14.7%	
4 risks	34	15.5%		26	16.6%	
5 risks	28	12.73%		23	14.7%	
6 risks	34	15.5%		28	17.8%	
7 risks	17	7.7%		13	8.3%	
8 risks	11	5.0%		9	5.7%	
9 risks	4	1.8%		1	0.6%	

Source: Nurse Family Partnership Program Data Set, Elmira Sample

Note: Table describes non-imputed data
[1]Data collected at intake
[2]Data collected at 32 weeks of pregnancy
[3]Data collected from intake to 32 weeks of pregnancy

Table 2.
Characteristics of children in full sample and sample in which DNA was collected

	Full Sample			DNA Sample		
	N	Mean(SD)/%	Range	N	Mean(SD)/%	Range
Child sex[1]	389			241		
Male		48.3%			48.1%	
Female		51.7%			51.9%	
Birth weight[1]	372	3206.7 (631.2)	567.0-4947.0	233	3248.1 (558.2)	1673.0-4947.0
Gestational age[1]	372	39.4 (2.7)	23.0-48.0	233	39.7 (2.1)	30.5 -48.0
IQ score[2]	325	102.8 (14.6)	61.0-160.0	226	102.4 (14.3)	64.0-149.0
IQ score[3]	302	109.6 (13.8)	68.0-160.0	214	109.5 (13.7)	68.0-154.0
Home environment (HOME) score[2]	315	38.3 (7.3)	16.0-52.0	219	37.8 (7.4)	16.0-51.0
Home environment (HOME) score[3]	309	39.2 (6.2)	19.0-54.0	218	39.0 (6.5)	19.0-54.0
Reports of child abuse and neglect[4]	380			237		
Yes		15.3%			15.6%	
No		84.7%			84.4%	
Glucocorticoid receptor genotype[5]						
rs6198				241		
A/A	n/a	n/a		173	71.8%	
A/G	n/a	n/a		55	22.8%	
G/G	n/a	n/a		8	3.3%	
Missing	n/a	n/a		5	2.1%	
rs6190				241		
A/A	n/a	n/a		1	0.4%	
A/G	n/a	n/a		14	5.8%	
G/G	n/a	n/a		223	92.5%	
Missing	n/a	n/a		3	1.3%	
rs2918417				241		
A/A	n/a	n/a		24	10.0%	
A/G	n/a	n/a		101	41.9%	
G/G	n/a	n/a		113	46.9%	
Missing	n/a	n/a		3	1.2%	
rs4244032				241		
A/A	n/a	n/a		160	66.4%	
A/G	n/a	n/a		65	26.9%	
G/G	n/a	n/a		12	5.0%	
Missing	n/a	n/a		4	1.7%	
rs12656106				241		
G/G	n/a	n/a		72	29.9%	
G/C	n/a	n/a		130	53.9%	
C/C	n/a	n/a		36	14.9%	
Missing	n/a	n/a		3	1.3%	
Cumulative Genetic Risk				236		
0 reactive G rs6190 and/or rs6198 alleles	n/a	n/a		14	5.9%	
1 reactive G rs6190 and/or rs6198 alleles	n/a	n/a		214	90.7%	
2 reactive G rs6190 and/or rs6198 alleles	n/a	n/a		8	3.4%	

Source: Nurse Family Partnership Program Data Set, Elmira Sample
Note: Table describes non-imputed data
[1]Data collected at child birth
[2]Data collected at age 3 years
[3]Data collected at age 4 years
[4]Data collected from birth to 4 years
[5]Data collected at age 27 years

Table 3.
Correlations of individual risk factors from maternal cumulative risk index

	High school drop-out	Unemployed	Unmarried	Teenage mother	Non-White	Household income below 1977 poverty line	No support network	Higher number of members in household	Paternal or maternal criminal engagement	Homeless	Relationship problems	General life anxiety
High school drop-out	1.00											
Unemployed	0.31***	1.00										
Unmarried	0.29***	0.17***	1.00									
Teenage mother	0.50***	0.28***	0.27***	1.00								
Non-White	0.16***	0.09***	0.18***	0.11***	1.00							
Household income below 1977 poverty line	0.21***	0.27***	0.28***	0.19***	0.17***	1.00						
No support network	0.10***	0.04	0.05*	0.04*	0.03	0.04	1.00					
Higher number of members in household	0.08***	0.04*	-0.04	0.12***	0.03	-0.07***	-0.07***	1.00				
Paternal or maternal criminal engagement	0.09***	0.08***	0.11***	0.05**	-0.05*	0.12***	0.03	0.01	1.00			
Homeless	0.07***	0.00	0.04	0.00	-0.03	0.08***	-0.03	-0.01	0.28***	1.00		
Relationship problems	0.21***	0.09***	0.16***	0.11***	0.00	0.12***	0.01	-0.09***	0.41***	0.21***	1.00	
General life anxiety	0.08***	0.05**	0.11***	0.10***	0.03	0.10***	-0.11***	-0.13***	0.06**	0.06**	0.18***	1.00

Source: Nurse Family Partnership Program Data Set, Elmira Sample

*p<.05, **p≤.01, ***p≤.001

Note: Imputed data; Maternal locus of control was originally included in the cumulative risk index but validity of the measure proved questionable.

Note: Mean VIF = 1.19

Table 4.
Correlations of maternal cumulative risk index and individual risk factors with child IQ at age 3 and 4 years

	IQ score at age 3 years	IQ score at age 4 years	VIF
Maternal cumulative risk index	-0.24***	-0.31***	
High school drop-out	-0.17***	-0.18***	1.44
Unemployed	-0.12***	-0.17***	1.15
Unmarried	-0.02	-0.07**	1.24
Teenage mother	-0.13***	-0.20***	1.37
Non-White	-0.14***	-0.17***	1.08
Household income below 1977 poverty line	-0.12***	-0.15***	1.24
No support network	-0.14***	-0.09***	1.04
Higher number of members in household	-0.07***	-0.17***	1.10
Paternal or maternal criminal engagement	-0.13***	-0.08***	1.20
Homeless	-0.04	-0.09***	1.11
Relationship problems	-0.12***	-0.14***	1.22
General life anxiety	-0.04	-0.05*	1.11

Source: Nurse Family Partnership Program Data Set, Elmira Sample
*p<.05, **p≤.01, ***p≤.001
Note: Imputed data

Table 5.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without (Model 1) and with (Model 2) postnatal influences in full sample

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*B*
Maternal cumulative risk	-1.93	***	0.36	-0.30	-1.01	**	0.37	-0.16
Treatment group	1.71		1.52	0.06	0.60		1.41	0.02
Maternal smoking	-0.10		0.09	-0.06	-0.00		0.09	-0.00
NARS	0.05		0.05	0.06	0.03		0.04	0.04
Child sex	-2.97	*	1.51	-0.11	-3.06	*	1.40	-0.11
Reports of child abuse and neglect	n/a		n/a	n/a	-4.33	*	1.98	-0.12
Caldwell EC-HOME	n/a		n/a	n/a	0.79	***	0.15	0.36
F Statistic	7.53 (5, 281.6)	***			13.06 (7, 260.2)	***		
Total R^2	0.12				0.26			
n	302				302			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample
Note: Imputed data

Table 6.
Multiple regressions of Stanford-Binet at age 4 years on individual maternal risks during pregnancy without (Model 1) and with (Model 2) postnatal influences in full sample

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*B*
Higher numbers of members in household	-5.80	**	2.05	-0.16	-4.72	*	1.94	-0.13
Household income below 1977 poverty line	-2.13		1.83	-0.07	-1.05		1.71	-0.04
Unemployed	-2.38		1.87	-0.08	-1.68		1.72	-0.06
Teenage Mother	-3.05		1.80	-0.11	-2.22		1.70	-0.08
High school drop-out	-0.21		1.86	-0.01	1.24		1.75	0.04
Unmarried	1.81		1.75	-0.06	1.47		1.61	0.05
Non-White	-6.87	**	2.64	-0.15	-6.38	**	2.53	-0.14
No support network	-4.70	*	2.44	-0.11	-3.12		2.29	-0.07
Paternal or maternal criminal engagement	-0.99		3.14	-0.02	0.53		2.77	0.01
Homeless	-4.00		4.21	-0.06	-4.09		3.79	-0.07
Relationship problems	-2.11		1.77	-0.07	-1.16		1.73	-0.04
General life anxiety	-1.67		1.82	-0.05	-1.38		1.69	-0.04
Treatment group	1.45		1.54	0.05	0.51		1.44	0.01
Maternal cigarettes per day	-0.16		0.10	-0.10	-0.07		0.09	-0.04
NARS	0.04		0.05	0.04	0.03		0.04	0.03
Child sex	-2.96	*	1.53	-0.11	-3.01	*	1.42	-0.11
Reports of child abuse and neglect	n/a		n/a	n/a	-5.43	**	2.05	-0.15
Caldwell EC-HOME	n/a		n/a	n/a	0.73	***	0.15	0.33
F Statistic	3.05 (17, 274.1)	***			5.53 (19, 271.0)	***		
Total R^2	0.17				0.29			
n	302				302			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample
Note: Imputed data

Table 7.
Frequency (%) of rs6190 within each level of maternal cumulative risk

	rs6190[2]				
Number of Maternal Risks During Pregnancy[1]	A/A	A/G	G/G	Missing	Total
0	0	1 (10.0)	1 (0.7)	0	2 (1.3)
1	0	0	10 (6.9)	0	10 (6.4)
2	0	3 (30.0)	19 (13.2)	0	22 (14.0)
3	0	2 (20.0)	21 (14.6)	0	23 (14.7)
4	0	1 (10.0)	25 (17.4)	0	26 (16.5)
5	0	0	23 (16.0)	0	23 (14.7)
6	0	2 (20.0)	24 (16.7	2 (100.0)	28 (17.8)
7	1 (100.0)	1 (10.0)	11 (7.6)	0	13 (8.3)
8	0	0	9 (6.3)	0	9 (5.7)
9	0	0	1 (0.6)	0	1 (0.6)
Total	1 (100.0)	10 (100.0)	144 (100.0)	2 (100.0)	157 (100.0)

Source: Nurse Family Partnership Program Data Set, Elmira Sample
[1]Data collected from intake to child birth
[2]Data collected at child age 27 years

Table 8.
Frequency (%) of rs6198 within each level of maternal cumulative risk

	rs6198[2]				
Number of Maternal Risks During Pregnancy[1]	A/A	A/G	G/G	Missing	Total
0	0	1 (2.9)	1 (16.7)	0	2 (1.3)
1	5 (4.4)	3 (8.8)	1 (16.7)	1 (25.0)	10 (6.4)
2	13 (11.5)	7 (20.6)	1 (16.7)	1 (25.0)	22 (14.1)
3	18 (15.9)	4 (11.8)	1 (16.7)	0	23 (14.7)
4	16 (14.2)	9 (26.5)	1 (16.6)	0	26 (16.6)
5	20 (17.7)	2 (5.9)	1 (16.6)	0	23 (14.7)
6	22 (19.5)	4 (11.8)	0	2 (50.0)	28 (17.8)
7	11 (9.7)	2 (5.9)	0	0	13 (8.3)
8	7 (6.2)	2 (5.8)	0	0	9 (5.6)
9	1 (0.9)	0	0	0	1 (0.5)
Total	113 (100.0)	34 (100.0)	6 (100.0)	4 (100.0)	157 (100.0)

Source: Nurse Family Partnership Program Data Set, Elmira Sample
[1]Data collected from intake to child birth
[2]Data collected at child age 27 years

Table 9.
Multiple regressions of gestational age and birth weight on maternal cumulative risk during pregnancy.

	Gestational age (Full sample)			Birth weight (Full sample)			Birth weight (DNA sample)		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*B*
Maternal cumulative risk	-0.17 *	0.07	-0.13	-47.49 **	16.32	-0.16	-47.17 **	16.32	-0.17
Treatment group	-0.24	0.29	-0.04	-32.04	64.37	-0.03	9.99	72.27	0.01
Maternal smoking	0.01	0.02	0.02	-10.39 **	3.61	-0.15	-10.89 **	3.60	-0.17
NARS	0.00	0.01	0.01	0.98	1.87	0.03	0.89	2.13	0.03
Child sex	-0.07	0.28	-0.01	95.77	64.04	0.08	95.50	72.12	0.09
Total R^2	0.02			0.06			0.07		
n	372			372			233		

*p≤.05, **p≤.01
Source: Nurse Family Partnership Elmira Sample
Note: Gestational age was not significant in the restricted sample.
Note: Imputed data

Table 10.
Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy without (Model 1) and with (Model 2) postnatal influences in full sample

	IQ score at age 3 years					
	Model 1			Model 2		
	B	*SE B*	*β*	*B*	*SE B*	*B*
Maternal cumulative risk	-1.56 ***	0.37	-0.24	-1.02 **	0.37	-0.16
Treatment group	1.34	1.58	0.05	0.69	1.56	0.02
Maternal cigarettes per day	-0.14	0.10	-0.08	-0.11	0.09	-0.06
NARS	0.01	0.05	0.01	-0.04	0.05	-0.05
Child sex	-2.21	1.58	-0.08	-2.01	1.56	-0.07
Caldwell EC-HOME	n/a	n/a	n/a	0.67 ***	0.11	0.33
Total R^2	0.07			0.17		
n	325			302		

*p≤.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample
Note: With respect to the association of maternal cumulative risk during pregnancy and IQ at 3 years of age, the mediation effect of low birth weight was significant, but small (7.6%). There was no effect of gestational age.
Note: Imputed data

Table 11.
Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy without (Model 1) and with (Model 2) postnatal influences in DNA sample

	IQ score at age 3 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*B*
Maternal cumulative risk	-1.61	***	0.47	-0.24	-1.06	*	0.45	-0.16
Treatment group	-0.06		1.87	-0.00	-0.35		1.78	-0.01
Maternal cigarettes per day	-0.17		0.11	-0.10	-0.10		0.11	-0.06
NARS	-0.03		0.05	-0.04	-0.07		0.05	-0.09
Child sex	-2.23		1.88	-0.08	-1.72		1.78	-0.06
Caldwell EC-HOME	n/a		n/a	n/a	0.72	***	0.13	0.38
Total R^2	0.07				0.21			
n	226				212			

*p≤.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample
Note: With respect to the association of maternal cumulative risk during pregnancy and IQ at 3 years of age, the mediation effect of low birth weight was significant, but small (8.9%). There was no effect of gestational age.
Note: Imputed data

Table 12.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without (Model 1) and with (Model 2) postnatal influences in full sample

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*B*
Maternal cumulative risk	-1.93	***	0.36	-0.30	-1.01	**	0.37	-0.16
Treatment group	1.71		1.52	0.06	0.60		1.41	0.02
Maternal cigarettes per day	-0.10		0.09	-0.06	-0.00		0.09	-0.00
NARS	0.05		0.05	0.06	0.03		0.04	0.04
Child sex	-2.97	*	1.51	-0.11	-3.06	*	1.40	-0.11
Reports of child abuse and neglect	n/a		n/a	n/a	-4.33	*	1.98	-0.12
Caldwell EC-HOME	n/a		n/a	n/a	0.79	***	0.15	0.36
Total R^2	0.12				0.26			
n	302				302			

*p<.05, **p≤.01, ***p≤.001
Note: With respect to the association of maternal cumulative risk during pregnancy and IQ at 4 years of age, the mediation effect of low birth weight was significant, but small (3.1%). There was no effect of gestational age.
Source: Nurse Family Partnership Elmira Sample
Note: Imputed data

Table 13.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without (Model 1) and with (Model 2) postnatal influences in DNA sample

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*B*
Maternal cumulative risk	-1.98	***	0.45	-0.30	-1.14	**	0.44	-0.17
Treatment group	1.42		1.81	0.05	0.90		1.67	0.03
Maternal cigarettes per day	-0.12		0.11	-0.07	-0.01		0.10	-0.01
NARS	0.00		0.05	0.01	0.00		0.05	0 .00
Child sex	-2.33		1.82	-0.09	-1.61		1.41	-0.06
Reports of child abuse and neglect	n/a		n/a	n/a	-3.30		2.31	-0.09
Caldwell EC-HOME	n/a		n/a	n/a	0.82	***	0.14	0.39
Total R^2	0.11				0.26			
n	214				214			

*p<.05, **p≤.01, ***p≤.001
Note: With respect to the association of maternal cumulative risk during pregnancy and IQ at 4 years of age, the mediation effect of low birth weight was significant, but small (8.2%). There was no effect of gestational age.
Source: Nurse Family Partnership Elmira Sample
Note: Imputed data

Table 14.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without (Model 1), inclusion of birthweight (Model 2), and addition of (Model 3) HOME score in full sample

	IQ score at age 4 years											
	Model 1				Model 2				Model 3			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.93	***	0.36	-0.30	-1.88	***	0.37	-0.29	-1.00	**	0.37	-0.16
Treatment group	1.71		1.52	0.06	1.68		1.52	0.06	0.67		1.42	0.02
Maternal smoking	-0.10		0.09	-0.06	-0.08		-0.09	-0.05	-0.01		0.09	-0.01
NARS	0.05		0.05	0.06	0.04		0.05	0.05	0.03		0.04	0.03
Child sex	-2.97	*	1.51	-0.11	-3.15	*	1.53	-0.11	-3.17	*	1.42	-0.11
Birthweight	n/a		n/a	n/a	0.00		0.00	0.05	0.00		0.00	0.02
Caldwell EC-HOME	n/a		n/a	n/a	n/a		n/a	n/a	0.84	***	0.14	0.39
Total R^2	0.12				0.12				0.24			
n	302				302				302			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample
Note: Imputed data

Table 15. Maternal risk during pregnancy by mean IQ at ages 3 and 4 years in DNA sample

Maternal cumulative risk	IQ at age 3 years	IQ at age 4 years
Low (4 risks or fewer)	105.20	113.00
High (5 risks or more)	99.70	106.00
Average	102.40	109.50
n	226	214

Note: Imputed data
Source: Nurse Family Partnership Elmira Sample

Table 16. Multivariate repeated measures of maternal cumulative risk during pregnancy on change in IQ from 3 to 4 years

F statistic	6.48(2.0, 135.0)	p=0.002
Wilks' lambda	0.91	
Pillai's trace	0.09	
Lawley-Hotelling trace	0.10	
Roy's largest root	0.10	
n	138	

Note: Imputed data
Source: Nurse Family Partnership Elmira Sample

Figure 2. HapMap of Glucocorticoid Receptors rs6198, rs6190, rs2918417, and rs4244032

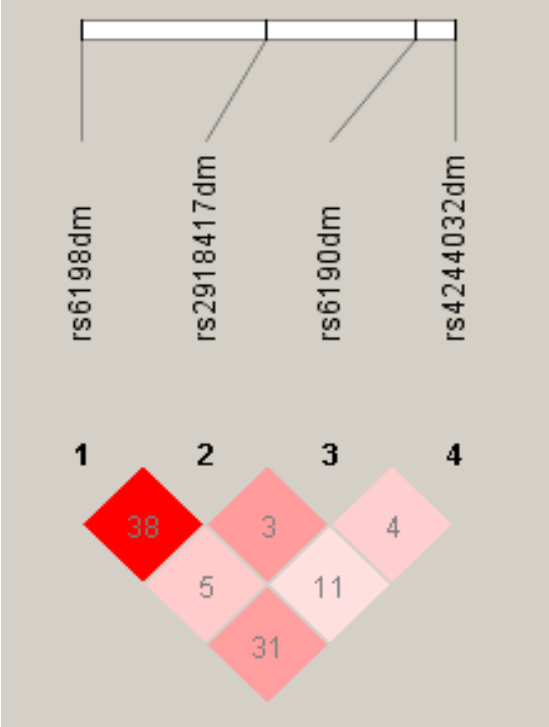


Table 17.

Multiple regressions of birth weight on maternal cumulative risk during pregnancy (Model 1) and controlling for rs2918417 (Model 2), rs4244032 (Model 3), rs6198 (Model 4) and rs6190 (Model 5), respectively

	Birth weight														
	Model 1			Model 2			Model 3			Model 4			Model 5		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Maternal cumulative risk	-58.99 **	21.53	-0.22	-60.36 **	21.59	-0.22	-63.18 **	21.66	-0.23	-51.84 *	22.04	-0.19	-62.30 **	21.39	-0.23
Treatment group	40.62	86.26	0.04	40.95	86.60	0.04	50.50	86.54	0.05	34.65	86.07	0.03	53.61	86.77	0.05
Maternal smoking	-9.63	5.13	-0.15	-10.16 *	5.13	-0.16	-9.95	5.16	-0.16	-9.83	5.11	0.16	-10.16 *	5.13	-0.16
NARS	0.81	2.48	0.03	0.60	2.45	0.02	0.73	2.49	0.02	0.87	2.47	0.03	0.67	2.50	0.02
Child sex	40.66	86.75	0.04	24.60	86.27	0.02	30.83	87.01	0.03	41.86	86.45	0.04	32.98	86.94	0.03
Rs2918417 (A/G and A/A)	n/a	n/a	n/a	48.84	87.01	0.04	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Rs4244032 (A/G and G/G)	n/a	n/a	n/a	n/a	n/a	n/a	-45.72	91.69	-0.04	n/a	n/a	n/a	n/a	n/a	n/a
Rs6198 (A/G and G/G)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	141.8	100.1	0.12	n/a	n/a	n/a
Rs6190 (A/G and A/A)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	-37.90	170.2	-0.02
Total R^2	0.08			0.08			0.08			0.09			0.08		
n	153			155			154			153			155		

*p≤.05, **p≤.01, ***p≤.001

Note: No change in significance with gene and risk interactions

Source: Nurse Family Partnership Elmira Sample

Table 18.

Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy without and with postnatal influences (Models 1 and 2) and rs6198 without and with postnatal influences (Models 3 and 4)

	IQ score at age 3 years															
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.76	**	0.60	-0.24	-0.82		0.58	-0.11	-1.79	**	0.62	-0.25	-0.84		0.60	-0.12
Treatment group	-0.83		2.44	-0.03	-0.44		2.24	-0.01	-0.80		2.45	-0.03	-0.42		2.26	-0.01
Maternal smoking	-0.23		0.13	-0.13	-0.13		0.14	-0.07	-0.23		0.15	-0.13	-0.13		0.14	-0.07
NARS	-0.11		0.07	-0.13	-0.16	**	0.07	-0.20	-0.11		0.07	-0.13	-0.17	**	0.07	-0.20
Child sex	-2.86		2.46	-0.10	-2.35		2.26	-0.08	-2.87		2.47	-0.10	-2.36		2.27	-0.08
Caldwell EC-HOME	n/a		n/a	n/a	0.82	***	0.16	0.42	n/a		n/a	n/a	0.82	***	0.16	0.42
rs6198 (A/G and G/G)	n/a		n/a	n/a	n/a		n/a	n/a	-0.59		2.81	-0.02	-0.42		2.59	-0.01
Total R^2	0.09				0.24				0.09				0.24			
N	142				142				142				142			

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Note: Models 1 and 2 are imputed.

Note: A/G and G/G genotypes run separately were not significant. Also, rs6198 defined by per allele risk was not significant.

Table 19.
Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy with rs6198 and moderation effects without and with postnatal influences (Models 1 and 2)

	IQ score at age 3 years					
	Model 1			Model 2		
	B	*SE B*	*β*	*B*	*SE B*	*β*
Maternal cumulative risk	-1.29	0.73	-0.17	-0.51	0.69	-0.07
Treatment group	-0.01	2.44	-0.00	-0.20	2.27	-0.01
Maternal smoking	-0.22	0.15	-0.12	-0.11	0.14	-0.06
NARS	-0.12	0.07	-0.15	-0.17 **	0.07	-0.20
Child sex	-2.42	2.45	-0.08	-2.34	2.27	-0.08
Caldwell EC-HOME	n/a	n/a	n/a	0.80 ***	0.16	0.41
rs6198 (A/G and G/G)	6.76	5.96	0.20	4.20	5.52	0.13
rs6198 (A/G and G/G)*risk	-1.83	1.36	-0.24	-1.19	1.26	-0.16
Total R^2	0.10			0.24		
n	145			142		

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Figure 3. Maternal Cumulative Risk during Pregnancy and IQ at Age 3 Years without Postnatal Controls in the presence of rs6198 A/G and G/G vs. A/A Genotypes in Children

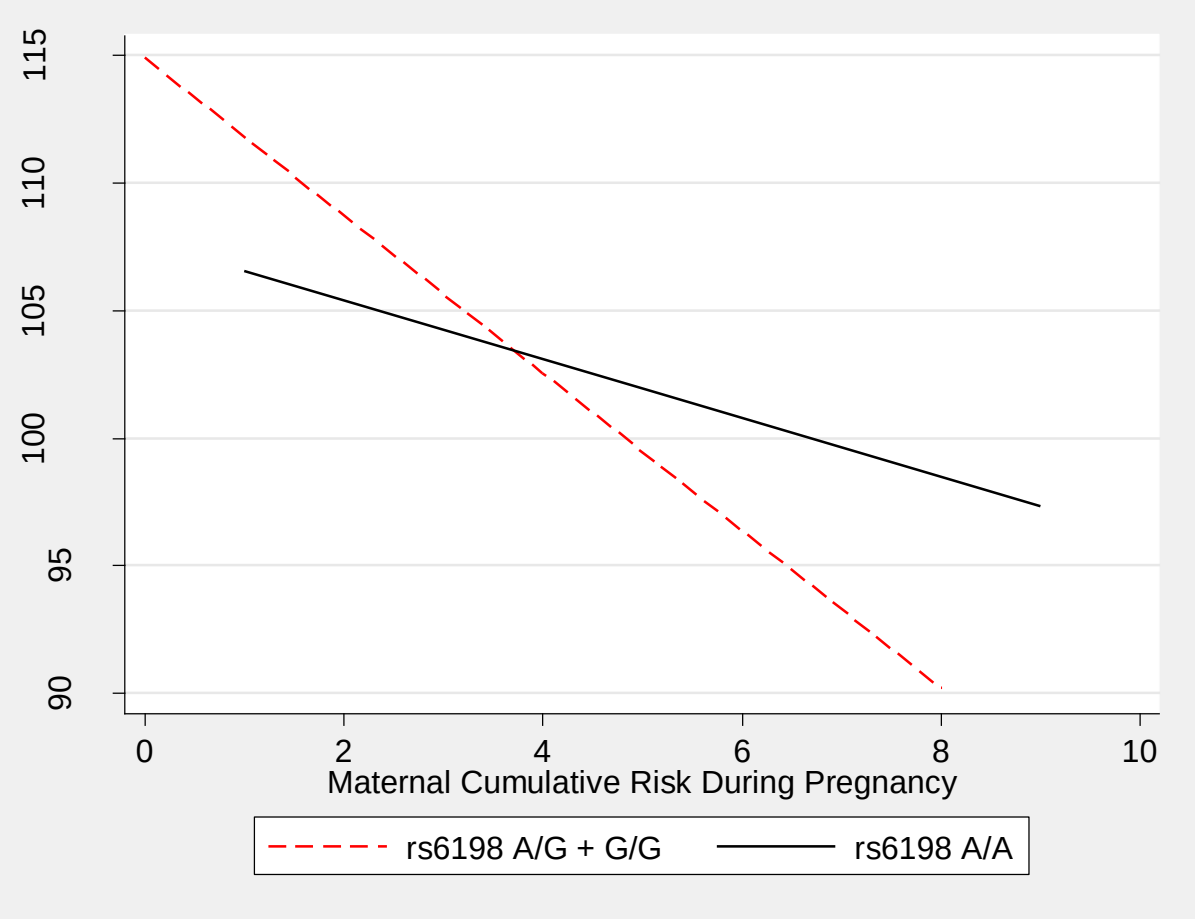


Table 20.

Summary of effects of maternal cumulative risk on IQ at age 3 years with presence of glucocorticoid receptor rs6198 genotypes

	A/A		A/G and G/G		
	B	*SE B*	*B*		*SE B*
Effect of maternal cumulative risk on IQ at age 3 years	-1.29	0.73	-3.11	**	1.14
IQ at age 3 years	n/a	n/a	6.76		5.96

Note: Model run without postnatal controls

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Table 21.

Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without and with postnatal influences (Models 1 and 2) and rs6198 per allele risk without and with postnatal influences (Models 3 and 4)

	IQ score at age 4 years															
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-2.62	***	0.59	-0.36	-1.30	*	0.56	-0.18	-2.60	***	0.60	-0.36	-1.32	*	0.57	-0.18
Treatment group	0.82		2.34	0.03	1.31		2.05	0.05	0.81		2.33	0.03	1.31		2.06	0.05
Maternal smoking	-0.21		0.14	-0.12	-0.03		0.13	-0.02	-0.21		0.14	-0.12	0.03		0.13	0.02
NARS	-0.04		0.07	0.04	-0.02		0.05	-0.02	-0.04		0.07	-0.04	-0.02		0.06	-0.02
Child sex	-0.75		2.36	-0.03	0.68		2.06	0.02	-0.74		2.36	-0.03	0.67		2.07	0.02
Reports of child abuse and neglect	n/a		n/a	n/a	-7.03	*	3.00	-0.17	n/a		n/a	n/a	-6.98	*	3.02	-0.17
Caldwell EC-HOME	n/a		n/a	n/a	1.07	***	0.18	0.47	n/a		n/a	n/a	1.08	***	0.18	0.48
rs6198 per allele risk	n/a		n/a	n/a	n/a		n/a	n/a	0.33		2.33	0.01	-0.51		2.45	-0.02
Total R^2	0.14				0.36				0.14				0.36			
N	137				137				138				137			

*p<.05, **p≤.01, ***p≤.001

Note: Models 1 and 2 are imputed.

Source: Nurse Family Partnership Elmira Sample

Table 22.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy and rs6198 per allele risk with interaction effects without and with postnatal influences

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.90	**	0.67	-0.26	-0.67		0.62	-0.09
Treatment group	1.48		2.32	0.05	1.94		2.04	0.07
Maternal smoking	-0.17		0.14	-0.10	0.06		0.13	0.04
NARS	-0.04		0.07	-0.05	-0.02		0.06	-0.03
Child sex	-0.70		2.32	-0.02	0.71		2.03	0.02
Reports of child abuse and neglect	n/a		n/a	n/a	-7.02	*	2.97	-0.17
Caldwell EC-HOME	n/a		n/a	n/a	1.07	***	0.18	0.47
rs6198 per allele risk	10.37	*	5.00	0.37	8.97	*	4.35	0.32
rs6198*Maternal cumulative risk	-2.74	*	1.21	-0.40	-2.58	**	1.05	0.37
Total R^2	0.18				0.39			
n	138				137			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Figure 4. Maternal Cumulative Risk during Pregnancy and IQ at Age 4 Years in Children in presence of rs6198 A/A, A/G, and G/G Genotypes in Children without Postnatal Controls

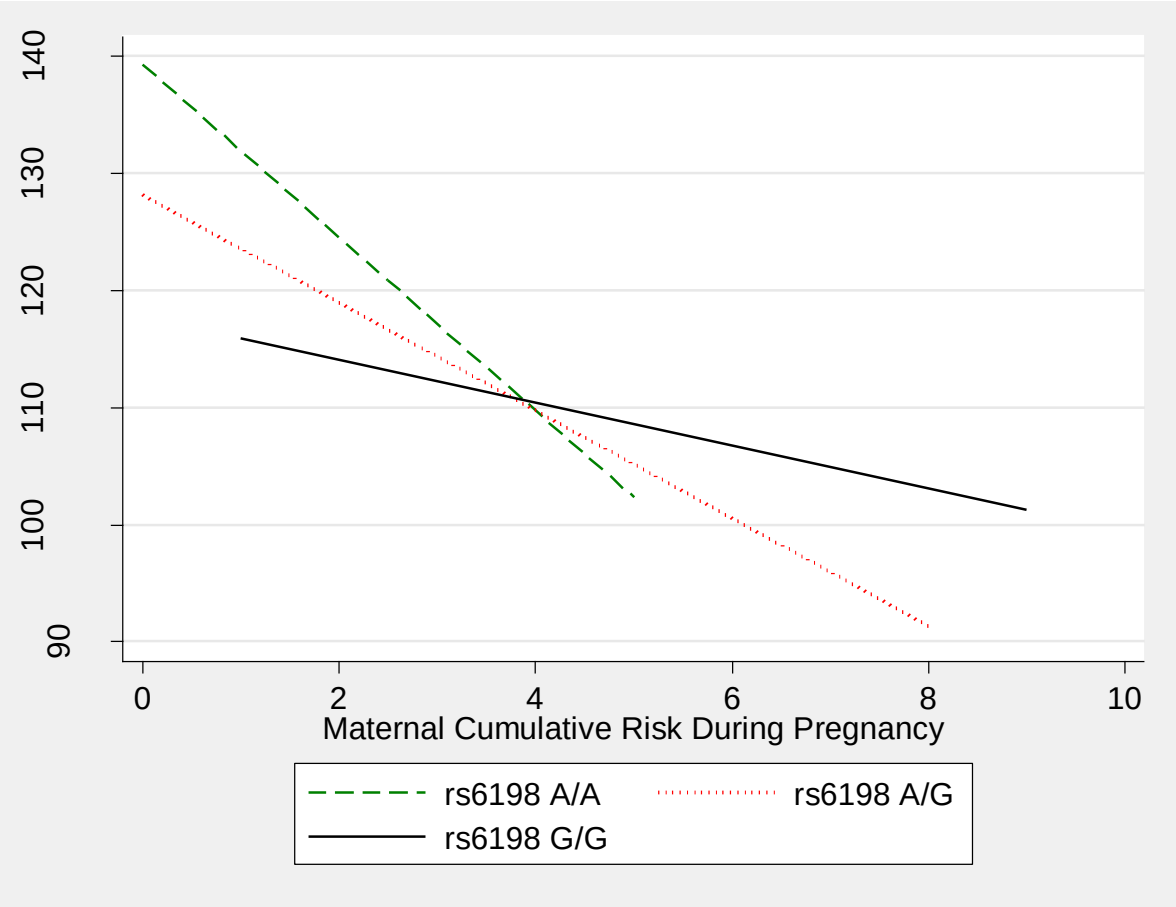


Table 23.

Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy and rs6198 genotypes with interaction effects without (Models 1 and 3) and with postnatal influences(Models2 and 4)

	IQ score at age 4 years															
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.89	**	0.68	-0.26	-0.65		0.63	-0.09	-5.08	***	1.20	-0.70	-3.61	***	1.08	-0.49
Treatment group	1.32		2.31	0.05	1.79		2.03	0.06	1.32		2.31	0.05	1.79		2.03	0.06
Maternal smoking	-0.17		0.14	-0.10	0.07		0.13	0.04	-0.17		0.14	-0.10	0.07		0.13	0.04
NARS	-0.04		0.07	-0.05	-0.02		0.06	-0.03	-0.04		0.07	-0.05	-0.02		0.06	-0.03
Child sex	-0.68		2.32	-0.02	0.73		2.03	0.03	-0.68		2.32	-0.02	0.73		2.03	0.03
Reports of child abuse and neglect	n/a		n/a	n/a	-7.01	*	2.97	-0.17	n/a		n/a	n/a	-7.01	*	2.97	-0.17
Caldwell EC-HOME	n/a		n/a	n/a	1.07	***	0.18	0.47	n/a		n/a	n/a	1.07	***	0.18	0.47
rs6198 (A/G and G/G)	11.61		6.13	0.35	10.06		5.34	0.30	n/a		n/a	n/a	n/a		n/a	n/a
rs6198 (A/G and G/G)* risk	-3.19	*	1.39	-0.42	-2.96	*	1.20	-0.39	n/a		n/a	n/a	n/a		n/a	n/a
rs6198 A/A	n/a		n/a	n/a	n/a		n/a	n/a	-11.61		6.13	-0.35	-10.06		5.34	-0.30
rs6198 A/A*risk	n/a		n/a	n/a	n/a		n/a	n/a	3.19	*	1.39	0.58	2.96	*	1.20	0.54
Total R^2	0.18				0.39				0.18				0.39			
N	138				137				138				137			

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Note: A/G and G/G genotypes were not significant when run separately or as interaction terms with cumulative risk.

Figure 5. Maternal Cumulative Risk during Pregnancy and IQ at Age 4 Years in Children in presence of rs6198 A/A vs. A/G and G/G Genotypes in Children without Postnatal Controls

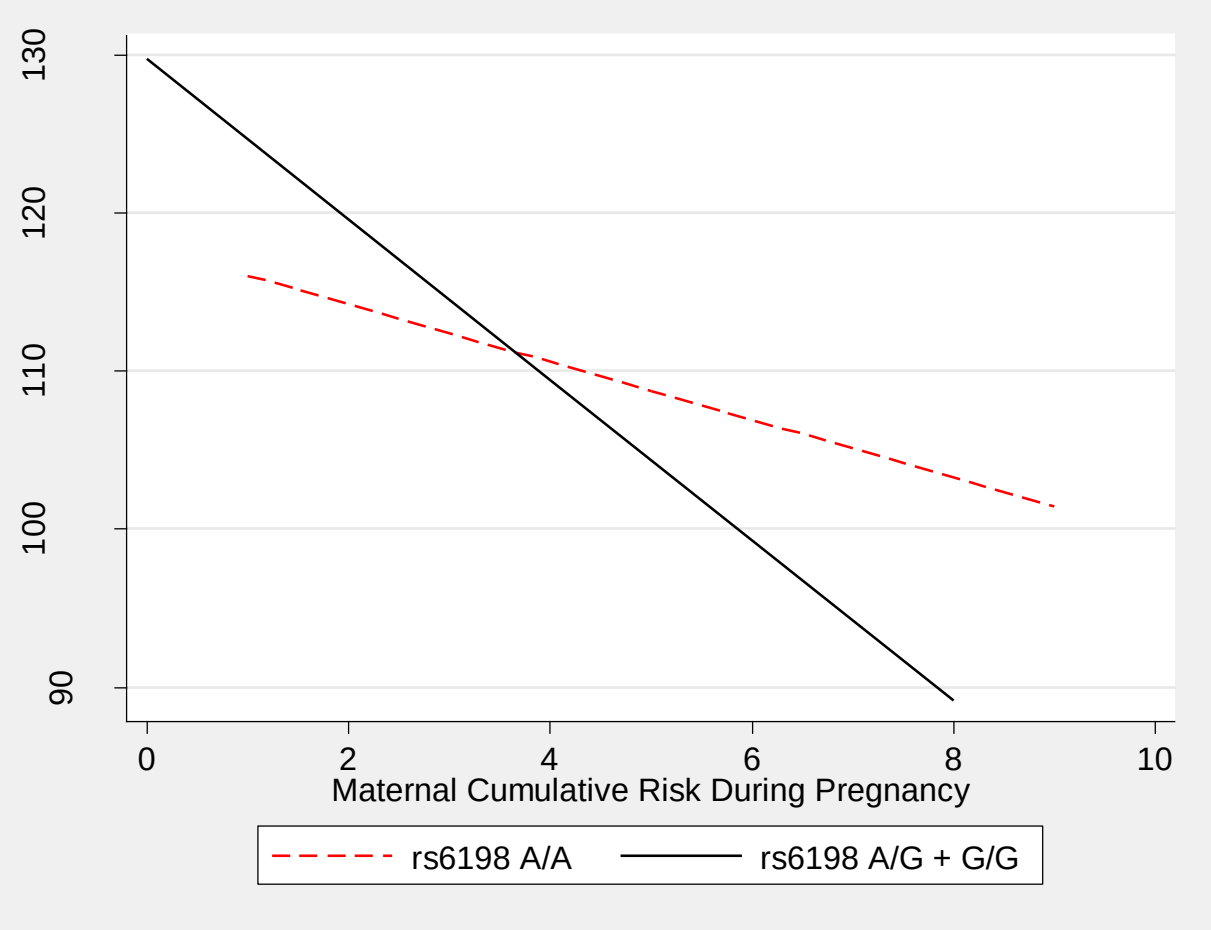


Table 24.
Summary of effects of maternal cumulative risk on IQ at age 4 years with presence of glucocorticoid receptor rs6198 genotypes

	A/A		A/G and G/G	
	B	*SE B*	*B*	*SE B*
Effect of maternal cumulative risk on IQ at age 4 years	-1.89 **	0.68	-5.08 ***	1.20
IQ at age 4 years	n/a	n/a	11.61	6.13

Note: Model run without postnatal controls
*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Table 25.

Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy without and with postnatal influences (Models 1 and 2) and per allele risk of rs6190 without and with postnatal influences (Models 3 and 4)

	IQ score at age 3 years														
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.74	**	0.59	-0.24	-0.82		0.57	-0.11	-1.85	**	0.58	-0.25	-0.89		0.57	-0.12
Treatment group	-1.13		2.42	-0.04	-0.65		2.22	-0.02	0.03		2.39	0.00	-0.33		2.24	-0.01
Maternal smoking	-0.22		0.15	-0.13	-0.12		0.14	-0.07	-0.25		0.15	-0.14	-0.13		0.14	-0.07
NARS	-0.11		0.07	-0.13	-0.17	**	0.06	-0.20	-0.13		0.07	-0.16	-0.17	**	0.07	-0.20
Child sex	-2.79		2.43	-0.09	-2.34		2.23	-0.08	-1.75		2.41	-0.06	-2.04		2.25	-0.07
Caldwell EC-HOME	n/a		n/a	n/a	0.83	***	0.16	0.42	n/a		n/a	n/a	0.79	***	0.16	0.40
rs6190 per allele risk	n/a		n/a	n/a	n/a		n/a	n/a	-4.25		3.85	-0.17	-4.25		3.85	0.09
Total R^2	0.09				0.24				0.08				0.25			
N	144				144				147				144			

*p<.05, **p≤.01, ***p≤.001

Note: Models 1 and 2 are imputed.

Source: Nurse Family Partnership Elmira Sample

Table 26.
Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy without and with postnatal influences with per allele risk of rs6190 and moderation effects without and with postnatal influences (Models 1 and 2)

	IQ score at age 3 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-2.06	***	0.61	-0.28	-1.11		0.59	-0.15
Treatment group	-0.05		0.39	-0.00	-0.41		2.23	-0.01
Maternal smoking	-0.24		0.15	-0.13	-0.12		0.14	-0.07
NARS	-0.13		0.07	-0.15	-0.17	**	0.06	-0.20
Child sex	-1.80		2.41	-0.06	-2.10		2.24	-0.07
Caldwell EC-HOME	n/a		n/a	n/a	0.79	***	0.16	0.40
rs6190 per allele risk	-17.45	*	0.64	-0.35	-13.59		8.03	-0.28
rs6190*risk	1.94		0.68	0.20	2.06		1.56	0.22
Total R^2	0.13				0.26			
n	147				144			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Please note: Interactions from this analysis were not able to be graphed due to an insufficient number of observations per allele.

Table 27.

Multiple regressions of Stanford-Binet at age 3 years on maternal cumulative risk during pregnancy and rs6190 genotypes without postnatal influence (Models 1, 2, 3) with interaction effects (Model 4).

	IQ score at age 3 years														
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.86	**	0.58	-0.26	-1.95	***	0.59	-0.27	-1.91	***	0.06	-0.26	-2.03	***	0.61	-0.28
Treatment group	-0.40		2.40	0.01	0.01		2.39	0.00	.0.07		2.38	0.00	-0.01		2.39	-0.00
Maternal smoking	-0.23		0.14	-0.13	-0.25		0.14	-0.14	-0.25		0.14	-0.14	-.024		0.15	-0.13
NARS	-0.13		0.07	-0.16	-0.13		0.07	-0.16	**-0.13**	*	0.07	-0.16	-0.13		0.07	-0.16
Child sex	-2.12		2.41	-0.07	-1.79		2.41	-0.06	**-1.72**		2.40	-0.06	-1.78		2.40	-0.06
rs6190 (A/G and A/A)	-10.77	*	4.55	-0.19	n/a		n/a	n/a	n/a		n/a	n/a	-16.23		8.99	-0.29
rs6190 A/G	n/a		n/a	n/a	-11.66	**	4.78	-0.20	n/a		n/a	n/a	n/a		n/a	n/a
rs6190 A/A	n/a		n/a	n/a	-2.96		14.51	-0.2	n/a		n/a	n/a	n/a		n/a	n/a
rs6190 G/G	n/a		n/a	n/a	n/a		n/a	n/a	10.87	*	4.56	0.19	n/a		n/a	n/a
rs6190 (A/G and A/A)*risk	n/a		n/a	n/a	n/a		n/a	n/a	n/a		n/a	n/a	1.40		2.02	-0.06
Total R^2	0.13				0.13				0.13				0.13			
N	144				147				147				147			

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Note: No interaction effects, No significance of rs6190 when postnatal HOME scores were included.

Figure 6. Maternal Cumulative Risk during Pregnancy and IQ at Age 3 Years without Postnatal Controls in the presence of rs6190 A/G and A/A vs. G/G Genotypes in Children

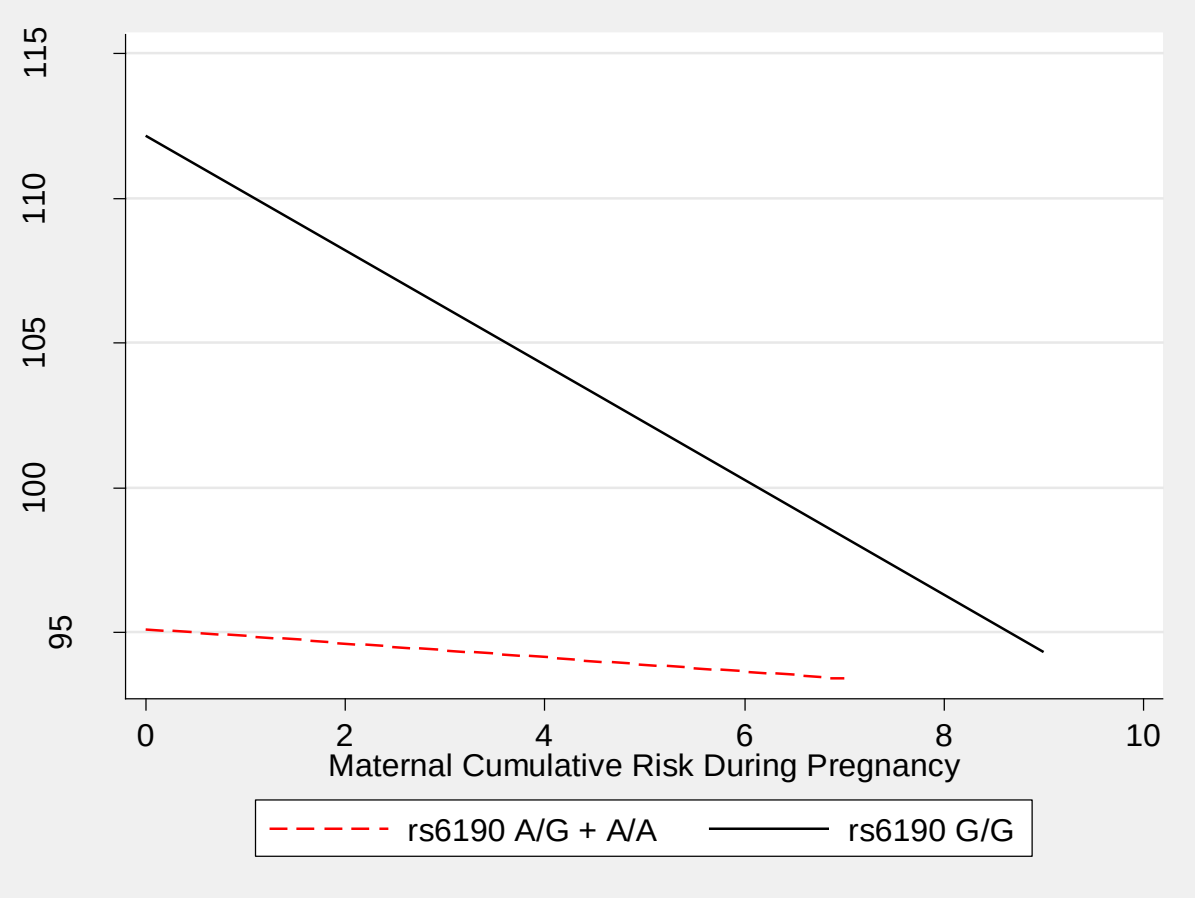


Table 28.
Summary of effects of maternal cumulative risk on IQ at age 3 years with presence of glucocorticoid receptor rs6190 genotypes.

	G/G			A/G and A/A	
	B		*SE B*	*B*	*SE B*
Effect of maternal cumulative risk on IQ at age 3 years	-2.03	***	0.61	-0.64	1.93
IQ at age 3 years	n/a		n/a	-16.23	8.99

Note: Model run without postnatal controls
*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Table 29.

Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy without and with postnatal influences (Models 1 and 2) and rs6190 per allele risk with interaction effects without and with postnatal influences (Models 3 and 4).

	IQ score at age 4 years															
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-2.54	***	0.58	-0.35	-1.27	*	0.55	-0.18	-2.56	***	0.58	-0.35	-1.31	*	0.56	-0.18
Treatment group	0.45		2.33	0.02	0.91		2.04	0.03	1.24		2.32	0.04	1.07		2.07	0.04
Maternal smoking	-0.19		0.14	-0.11	0.03		0.13	0.02	-0.20		0.14	-0.11	0.03		0.13	0.02
NARS	-0.03		0.07	-0.04	-0.02		0.06	-0.02	-0.04		0.07	-0.05	-0.02		0.06	-0.02
Child sex	-0.50		2.35	-0.02	0.76		2.05	0.03	0.03		2.33	0.00	0.81		2.06	0.03
Reports of child abuse and neglect	n/a		n/a	n/a	-6.90	*	3.01	-0.16	n/a		n/a	n/a	-6.80	*	3.02	-0.16
Caldwell EC-HOME	n/a		n/a	n/a	1.08	***	0.18	0.47	n/a		n/a	n/a	1.05	***	0.19	0.46
rs6190 per allele risk	n/a		n/a	n/a	n/a		n/a	n/a	-9.23	*	4.09	-0.18	-1.98		3.81	-0.04
rs6190*risk	n/a		n/a	n/a	n/a		n/a	n/a	n/a		n/a	n/a	n/a		n/a	n/a
Total R^2	0.14				0.36				0.17				0.36			
N	139				139				139				139			

*p<.05, **p≤.01, ***p≤.001

Note: Models 1 and 2 are imputed.

Source: Nurse Family Partnership Elmira Sample

Table 30.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy and rs6190 with interaction effects without and with postnatal influences (Models 1 and 2).

	IQ score at age 4 years							
	Model 1				Model 2			
	B		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-2.84	***	0.59	-0.39	-1.60	**	0.56	-0.22
Treatment group	1.44		2.29	0.05	1.28		2.04	0.04
Maternal smoking	-0.19		0.14	-0.11	0.04		0.13	0.02
NARS	-0.05		0.07	-0.06	-0.02		0.06	-0.03
Child sex	-0.21		2.30	-0.01	0.60		2.04	0.02
Reports of child abuse and neglect	n/a		n/a	n/a	-6.92	*	2.98	-0.17
Caldwell EC-HOME	n/a		n/a	n/a	1.06	***	0.19	0.46
rs6190 per allele risk	-25.36	**	9.72	-0.50	-19.34	*	8.63	-0.38
rs6190*risk	3.36		1.84	0.35	3.63	*	1.63	0.38
Total R^2	0.19				0.38			
n	140				139			

*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Please note: Interactions from this analysis were not able to be graphed due to an insufficient number of observations per rs6190 genotype.

Table 31.

Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy and rs6190 genotypes with interaction effects without (Models 1 and 3) and with postnatal influences (Models 2 and 4).

	IQ score at age 4 years															
	Model 1				Model 2				Model 3				Model 4			
	B		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-2.87	***	0.59	-0.40	-1.62	**	0.56	-0.22	-2.92	***	0.58	-0.40	-1.59	**	0.54	-0.22
Treatment group	1.39		2.28	0.04	1.24		2.02	0.04	1.39		2.28	0.05	1.54		1.97	0.05
Maternal smoking	-0.19		0.14	-0.11	0.06		0.13	0.04	-0.18		0.14	-0.10	0.10		0.12	0.06
NARS	-0.05		0.07	-0.06	-0.02		0.06	-0.03	-0.05		0.07	-0.06	-0.02		0.06	-0.03
Child sex	0.28		2.30	-0.01	0.48		2.01	0.02	-0.36		2.29	-0.01	0.62		1.96	0.02
Reports of child abuse and neglect	n/a		n/a	n/a	-7.50	**	2.96	-0.18	n/a		n/a	n/a	-8.64	**	2.94	-0.21
Caldwell EC-HOME	n/a		n/a	n/a	1.13	***	0.19	0.49	n/a		n/a	n/a	1.19	***	0.18	0.52
rs6190 (A/G and A/A)	-26.32	**	10.40	-0.45	-24.87	**	9.08	-0.43	n/a		n/a	n/a	n/a		n/a	n/a
rs6190 (A/G and A/A)*risk	3.73		2.31	0.29	5.87	**	2.04	0.45	n/a		n/a	n/a	n/a		n/a	n/a
rs6190 A/G	n/a		n/a	n/a	n/a		n/a	n/a	-29.64	**	11.08	-0.48	-32.93	***	9.50	-0.53
rs6190 A/G* risk	n/a		n/a	n/a	n/a		n/a	n/a	4.97		2.70	0.33	9.02	***	2.38	0.59
Total R^2	0.19				0.40				0.19				0.42			
n	140				139				140				139			

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Note: A/A genotype alone was not significant (n = 1).

Table 32.

Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy and rs6190 without interaction effects and without and with postnatal influences (Models 1 and 2) and with interaction effects without and with postnatal influences (Models 3 and 4).

	IQ score at age 4 years											
	Model 1			Model 2			Model 3			Model 4		
	B	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*	*B*	*SE B*	*β*
Maternal cumulative risk	-2.62 ***	0.57	-0.36	-1.32 *	0.56	-0.18	0.86	2.23	0.12	4.24 *	2.01	0.59
Treatment group	1.27	2.30	0.04	1.03	2.07	0.04	1.39	2.28	0.05	1.24	2.02	0.04
Maternal smoking	-0.20	0.14	-11.48	0.03	0.13	0.02	-0.19	0.14	-0.11	0.06	0.13	0.04
NARS	-0.05	0.07	-0.06	-0.02	0.06	0.02	-0.05	0.07	-0.06	-0.02	0.06	-0.03
Child sex	-0.04	2.30	0.00	0.81	2.06	0.03	-0.28	2.30	-0.01	0.48	2.01	0.02
Reports of child abuse and neglect	n/a	n/a	n/a	-6.78 *	3.03	-0.16	n/a	n/a	n/a	-7.50 **	2.96	-0.18
Caldwell EC-HOME	n/a	n/a	n/a	1.06 ***	0.19	0.46	n/a	n/a	n/a	1.13 ***	0.19	0.49
rs6190 G/G	11.28 *	4.70	0.19	1.90	4.46	0.03	26.32 **	10.40	-0.45	24.87 **	9.01	0.43
rs6190 G/G*risk	n/a	n/a	n/a	n/a	n/a	n/a	-3.73	2.31	-0.57	-5.87 **	2.04	-0.90
Total R^2	0.17			0.36			0.19			0.40		
N	140			139			140			139		

*p<.05, **p≤.01, ***p≤.001

Source: Nurse Family Partnership Elmira Sample

Figure 7. Maternal Cumulative Risk during Pregnancy and IQ at Age 4 Years in Children in presence of rs6190 G/G vs. A/G and A/A Genotypes in Children without Postnatal Controls

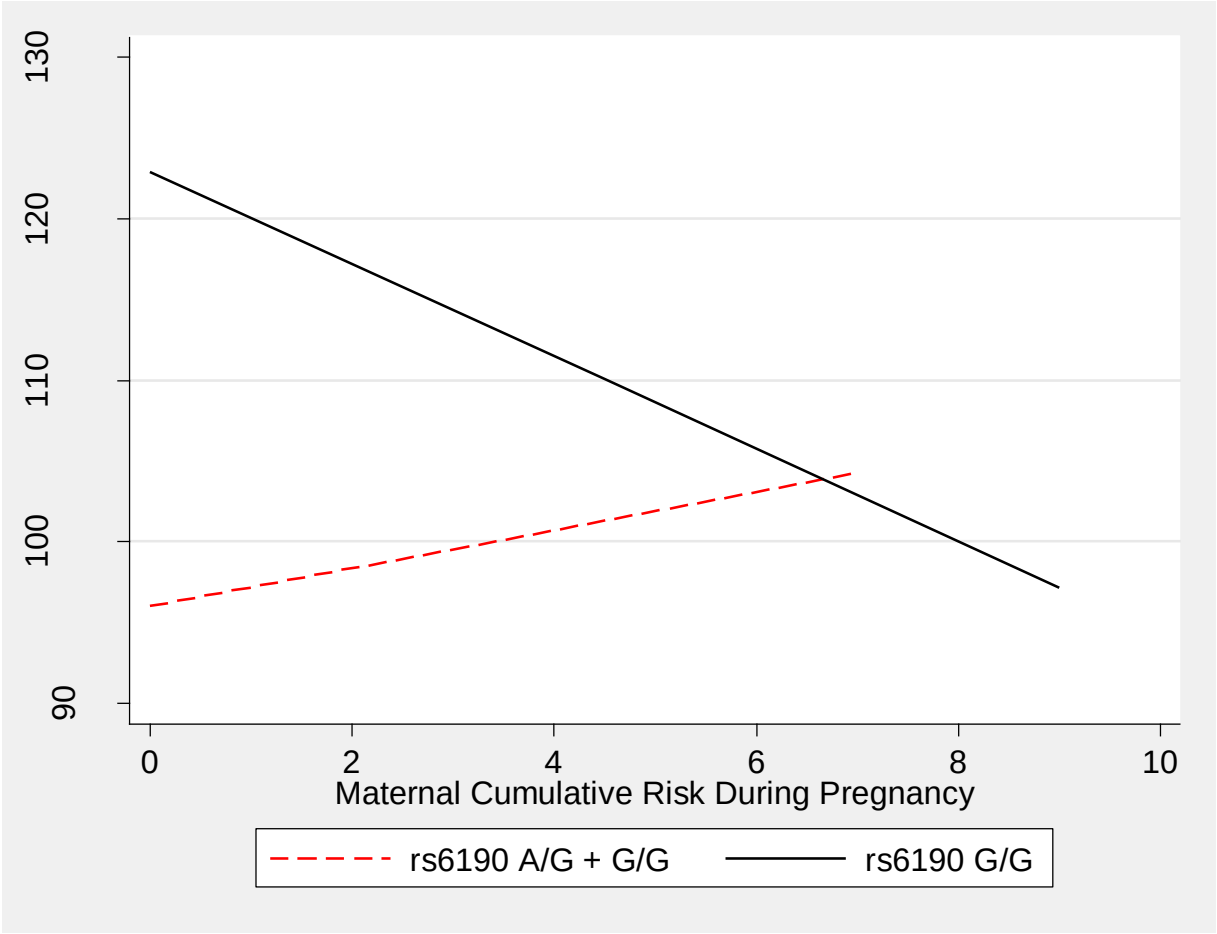


Table 33.
Summary of effects of maternal cumulative risk on IQ at age 4 years with presence of glucocorticoid receptor rs6190 genotypes.

	G/G		A/G and A/A	
	B	*SE B*	*B*	*SE B*
Effect of maternal cumulative risk on IQ at age 4 years	-2.87 ***	0.59	0.86	2.23
IQ at age 4 years	n/a	n/a	-26.32 **	10.40

Note: Model run without postnatal controls
*p<.05, **p≤.01, ***p≤.001
Source: Nurse Family Partnership Elmira Sample

Table 33.
Multiple regressions of Stanford-Binet at age 4 years on maternal cumulative risk during pregnancy with cumulative genetic risk, postnatal controls, and without and with interaction effects.

	IQ score at age 4 years							
	B		*SE B*	*β*	*B*		*SE B*	*β*
Maternal cumulative risk	-1.32	*	0.56	-0.18	2.97		1.84	0.41
Cumulative genetic risk	2.30		3.73	0.05	17.96	*	7.40	0.37
Treatment group	1.49		2.08	0.05	1.82		2.04	0.06
Maternal smoking	0.02		0.13	0.01	0.06		0.13	0.04
NARS	-0.02		0.06	0.01	-0.02		0.06	-0.03
Child sex	0.76		2.07	0.03	0.53		2.04	0.02
Reports of child abuse and neglect	-6.81	*	3.03	-0.16	-7.31	*	3.00	-0.18
Caldwell EC-HOME	1.04	***	0.19	0.46	1.12	***	0.19	0.49
Maternal cumulative risk*cumulative genetic reactivity	n/a		n/a	n/a	-4.33	*	1.78	-0.67
Total R^2	0.36				0.39			
n	137				137			

*p<.05, **p≤.01, ***p≤.001
Note: Because rs6198 A is reactive and protective in this analysis it is not included in cumulative genetic risk.
Note: There were no main effects or interaction effects at age 3 years.
Source: Nurse Family Partnership Elmira Sample

Figure 8. Maternal Cumulative Risk during Pregnancy and IQ at Age 4 Years in Children with Cumulative Genetic Risk in Children